IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants:	H. William Bosch et al.
Title:	NOVEL NIMESULIDE COMPOSITIONS
Appl. No.:	10/697,703
Filing Date:	10/31/2003
Examiner:	Sara CLARK
Art Unit:	1612
Confirmation Number:	8369

BRIEF ON APPEAL

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Sir:

This Appeal Brief is the second filed in the above-referenced application. Upon filing the first Appeal Brief on July 29, 2010, all rejections raised in the final Office Action dated February 18, 2010 were withdrawn. However, the Examiner reopened prosecution and issued a non-final Office Action on November 9, 2010, raising new grounds of rejection, which are addressed in this Appeal Brief. Appellants do not believe any fee is due. Authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

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FEDERAL CASES

In re KUBIN

561 F.3d 1351 (Fed. Cir. 2009)

In re Marek Z. KUBIN and Raymond G. Goodwin.

No. 2008-1184.

United States Court of Appeals, Federal Circuit.

April 3, 2009.

Background: Applicants for patents related to claimed biotechnology invention for isolating and sequencing of human gene that encoded particular domain of protein, specifically DNA molecules, or polynucleotides, encoding polypeptide known as Natural Killer Cell Activation Inducing Ligand (NAIL). The United States Patent and Trademark Office, Board of Patent Appeals and Interferences, 2007 WL 2070495, rejected claims as obvious and invalid for lack of written description. Applicants appealed.

Holding: The Court of Appeals, Rader, Circuit Judge, held that claimed gene sequence was unpatentably obvious in light of abundant prior art.

Affirmed.

1. Patents ⇐113(6)

Court of Appeals reviews factual findings by the Board of Patent Appeals and Interferences for lack of substantial evidence, and the Board's legal conclusions without deference.

2. Patents ⇐16.13

In determining patentability, obviousness of a claimed invention is a question of law based on underlying findings of fact. 35 U.S.C.A. § 103.

3. Patents ⇐16(2, 3), 36.1(1)

An analysis of obviousness to determine patentability must be based on several factual inquiries: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art at the time the invention was made, and (4) objective evidence of nonobviousness, if any. 35 U.S.C.A. § 103.

4. Patents ⇐16.13

The teachings of a prior art reference are underlying factual questions in the obviousness inquiry for patentability of a claimed invention. 35 U.S.C.A. § 103.

5. Patents ⇐36(3)

Board of Patent Appeals and Interferences' conclusion, in rejecting claims of patent application for isolating human gene sequence for natural killer cell activation inducing ligand (NAIL), that claimed sequence was obvious in light of abundant prior art, was supported by substantial evidence including that application disclosed use of standard biochemical methods outlined in prior art to isolate gene sequence for NAIL, that researcher of ordinary skill in art would have recognized that prior art discussed detailed protocol for identifying, isolating, and cloning equivalent of NAIL, that prior art did not teach away from combining its teachings with other references regarding gene sequence, and that skilled artisan would have had resoundingly reasonable expectation of success in deriving claimed invention in light of teachings of prior art. 35 U.S.C.A. § 103(a).

6. Patents ⇐16.5(1)

A prior art reference may be said to "teach away" when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the patent applicant. 35 U.S.C.A. § 103.

See publication Words and Phrases for other judicial constructions and definitions.

Patents ⇐328(2)

5,688,690. Cited as Prior Art.

Barbara R. Rudolph, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for appellants. With her on the brief were Herbert H. Mintz and Bart A. Gerstenblith. Of counsel was Stuart L. Watt, Wendy A. Whiteford and Gail A. Katz, Amgen Inc., of Thousand Oaks, CA, and Kathleen Fowler, of Seattle, WA.

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James J. Kelley, Eli Lilly and Company, of Indianapolis, IN, for amicus curiae Eli Lilly and Company. With him on the brief were MaryAnn Wiskerchen, Gregory A. Cox, Steven P. Caltrider and Robert A. Armitage.

Before RADER, FRIEDMAN, and LINN, Circuit Judges.

RADER, Circuit Judge.

Marek Kubin and Raymond Goodwin ("appellants") appeal from a decision of the Board of Patent Appeals and Interferences (the "Board") rejecting the claims of U.S. Patent Application Serial No. 09/667,859 ("'859 Application") as obvious under 35 U.S.C. § 103(a) and invalid under 35 U.S.C. § 112 ¶ 1 for lack of written description. *Ex parte Kubin*, No. 2007-0819, 83 U.S.P.Q.2d 1410 (B.P.A.I.2007) ("*Board Decision*"). Because the Board correctly determined that appellants' claims are unpatentably obvious, this court affirms.

I.

This case presents a claim to a classic biotechnology invention—the isolation and sequencing of a human gene that encodes a particular domain of a protein. This court provided a primer on the basics of this technology in *In re O'Farrell*, 853 F.2d 894, 895–99 (Fed.Cir.1988). Specifically, appellants claim DNA molecules ("polynucleotides") encoding a protein ("polypeptide") known as the Natural Killer Cell Activation Inducing Ligand ("NAIL").

Natural Killer ("NK") cells, thought to originate in the bone marrow, are a class of cytotoxic lymphocytes that play a major role in fighting tumors and viruses. NK cells express a number of surface molecules which, when stimulated, can activate cytotoxic mechanisms. NAIL is a specific receptor protein on the cell surface that plays a role in activating the NK cells.

The specification of the claimed invention recites an amino acid sequence of a NAIL polypeptide. The invention further isolates and sequences a polynucleotide that encodes a NAIL polypeptide. Moreover, the inventors trumpet their alleged discovery of a binding relationship between NAIL and a protein known as CD48. The NAIL-CD48 interaction has

important biological consequences for NK cells, including an increase in cell cytotoxicity and in production of interferon. Representative claim 73 of appellants' application claims the DNA that encodes the CD48-binding region of NAIL proteins:

> 73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

In other words, appellants claim a genus of isolated polynucleotides encoding a protein that binds CD48 and is at least 80% identical to amino acids 22-221 of SEQ ID NO:2—the disclosed amino acid sequence for the CD48-binding region of NAIL.

Appellants' specification discloses nucleotide sequences for two polynucleotides falling within the scope of the claimed genus, namely SEQ ID NO:1 and SEQ ID NO:3. SEQ ID NO: 1 recites the specific coding sequence of NAIL, whereas SEQ ID NO: 3 recites the full NAIL gene, including upstream and downstream noncoding sequences. The specification also contemplates variants of NAIL that retain the same binding properties:

> Variants include polypeptides that are substantially homologous to the native form, but which have an amino acid sequence different from that of the native form because of one or more deletions, insertions or substitutions. Particular embodiments include, but are not limited to, polypeptides that comprise from one to ten deletions, insertions or substitutions of amino acid residues, when compared to a native sequence.
>
> A given amino acid may be replaced, for example, by a residue having similar physiochemical characteristics. Examples of such conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another; substitutions of one polar residue for another, such as between Lys and Arg, Glu and Asp, or Gln and Asn; or substitutions of one aromatic residue for another, such as Phe, Trp, or Tyr for one another. Other conservative substitutions, e.g., involving substitutions of entire regions having similar hydrophobicity characteristics, are well known.

'859 Application at 26. However, the specification does not indicate any example variants of NAIL that make these conservative amino acid substitutions.

II.

The Board rejected appellants' claims as invalid under both § 103 and § 112. With regard to the § 112 rejection, the Board found the genus of nucleic acids of representative claim 73 unsupported by an adequate written description. First, the Board observed that although appellants had sequenced two nucleic acids falling within the scope of claim 73, they had not disclosed any variant species where amino acids 22-221 were different in any way from the disclosed SEQ ID NO:2 sequence. Thus, the Board concluded that appellants were not entitled to their genus claim of DNA molecules encoding proteins 80% identical to SEQ ID NO:2:

> [Appellants] have not described what domains of those sequences are correlated with the required binding to CD48, and thus have not described which of NAIL's amino acids can be varied and still maintain binding. Thus ... their Specification would not have shown possession of a sufficient number of sequences falling within their potentially large genus to establish possession of their claimed genus.

Without a correlation between structure and function, the claim does little more than define the claimed invention by

function. That is not sufficient to satisfy the written description requirement.

Board Decision at 16–17.

Regarding obviousness, the Board rejected appellants' claims over the combined teachings of U.S. Patent No. 5,688,690 ("Valiante") and 2 Joseph Sambrook et al., *Molecular Cloning: A Laboratory Manual* 43–84 (2d ed.1989) ("Sambrook"). The Board also considered, but found to be cumulative to Valiante and Sambrook, Porunelloor Mathew et al., *Cloning and Characterization of the 2B4 Gene Encoding a Molecule Associated with Non-MHC-Restricted Killing Mediated by Activated Natural Killer Cells and T Cells*, 151 J. Immunology 5328–37 (1993) ("Mathew").

Valiante discloses a receptor protein called "p38" that is found on the surface of human NK cells. Valiante teaches that the p38 receptor is present on virtually all human NK cells and "can serve as an activation marker for cytotoxic NK cells." '690 Patent col.3 ll.3–4; *see also id.* at col.5 ll.6–7 ("Stimulation of p38 results in activation of cytotoxicity"). Valiante also discloses and claims a monoclonal antibody specific for p38 called "mAB C1.7." The Board found (and appellants do not dispute) that Valiante's p38 protein is the same protein as NAIL. *Board Decision* at 4. A monoclonal antibody is an antibody that is mass produced in the laboratory from a single clone and that recognizes only one antigen. Monoclonal antibodies are useful as probes for specifically identifying and targeting a particular kind of cell.

Valiante teaches that "[t]he DNA and protein sequences for the receptor p38 may be obtained by resort to conventional methodologies known to one of skill in the art." '690 Patent col.7 ll.49–51.

For example, the receptor may be isolated by immunoprecipitation using the mAb C1.7. Alternatively, the receptor may be obtained by prokaryotic expression cloning, using the lambda phage gtll, which is described in detail in Sambrook et al, Molecular Cloning, A Laboratory Manual, 2d edit., Cold Spring Harbor, N.Y. (1989), pp. 2.43–2.84, incorporated by reference herein.

Additionally, as described in Example 12 below, the DNA sequence encoding the receptor can be obtained by the "panning" technique of screening a human NK cell library by eukaryotic expression cloning, of which several are known. Briefly, plasmids are constructed containing random sequences of a human NK cell library which are obtained by restriction digestion. Such libraries may be made by conventional techniques or may be available commercially.

Suitable cells, preferably mammalian cells, such as COS–1 cells, are transfected with the plasmids and the mAb C1.7 antibody employed to identify transfectants containing the receptor after repeated rounds of panning. The receptor insert in these cells is then identified and sequenced by conventional techniques, such as overlapping deletion fragments [Sambrook et al. cited above]. Other known techniques may also be employed to sequence the receptor and/or the mAb C1.7.

Id. at col.7 l.51–col.8 l.7. Example 12 of Valiante's patent further describes a five-step cloning protocol for "isolating and identifying the p38 receptor." *Id.* at col.18 l.6–col.19 l.28. Valiante discloses neither the amino acid sequence of p38 recognized by mAb C1.7 nor the polynucleotide sequence that encodes p38. Sambrook, incorporated by reference (as cited above) in Valiante, describes methods for molecular cloning. Sambrook does not discuss how to clone any particular gene, but provides detailed instructions on cloning materials and techniques.

The Mathew reference discloses a cell surface receptor protein called 2B4 "expressed on all NK ... cells." Mathew at 5328. Mathew discloses that 2B4 is involved in activating mouse NK cells, and further teaches the "chromosomal mapping, cloning, expression, and molecular characterization of the 2B4 gene." *Id.* at 5329. Further, Mathew teaches a monoclonal antibody, mAb 2B4, specific to 2B4, and a detailed cloning protocol for obtaining the sequence of the gene that codes for the 2B4 protein. *Id.* at 5328–330. The Board found that Mathew's signaling molecule 2B4 is the murine (mouse) version of Valiante's p38. *Board Decision* at 5. The Board viewed Mathew's teachings to be "cumulative to the teachings in Valiante and Sambrook and merely ... exemplary of how routine skill in the art can be utilized to clone and sequence the cDNA of a similar polypeptide." *Id.*

The Board found as a factual matter that appellants used conventional techniques "such as those outlined in Sambrook" to isolate and sequence the gene that codes for NAIL. *Id.* The Board also found that appellants' claimed DNA sequence is "isolated from a cDNA library ... using the commercial monoclonal antibody C1.7 ... disclosed by Valiante." *Id.* With regard to the amino acid sequence referred to as SEQ ID NO:2, the Board found that

> Valiante's disclosure of the polypeptide p38, and a detailed method of isolating its DNA, including disclosure of a specific probe to do so, i.e., mAb C1.7, established Valiante's possession of p38's amino acid sequence and provided a reasonable expectation of success in obtaining a polynucleotide encoding p38, a polynucleotide within the scope of Appellants' claim 73. (See Valiante, col.7, l.48 to col.8, l.7.)

Id. at 6. Because of NAIL's important role in the human immune response, the Board further found that "one of ordinary skill in the art would have recognized the value of isolating NAIL cDNA, and would have been motivated to apply conventional methodologies, such as those disclosed in Sambrook and utilized in Valiante, to do so." *Id.* at 6–7.

Based on these factual findings, the Board turned to the legal question of obviousness under § 103. Invoking the Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007), the Board concluded that appellants' claim was " 'the product not of innovation but of ordinary skill and common sense,' leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it." *Board Decision* at 9 (citing *KSR*, 550 U.S. at 421, 127 S.Ct. 1727).

Appellants appeal the Board's decisions both as to obviousness and written description. This court has jurisdiction under 28 U.S.C. § 1295(a)(4) and 35 U.S.C. § 141.

III.

[1] This court reviews the Board's factual findings for lack of substantial evidence, and its legal conclusions without deference. *In re Gartside*, 203 F.3d 1305, 1315 (Fed.Cir.2000).

[2–4] Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). The teachings of a prior art reference are underlying factual questions in the obviousness inquiry. *See*

Para-Ordnance Mfg., Inc. v. SGS Imp. Int'l, Inc., 73 F.3d 1085, 1088 (Fed.Cir. 1995).

A.

As a factual matter, the Board concluded that appellants' methodology of isolating NAIL DNA was essentially the same as the methodologies and teachings of Valiante and Sambrook. Appellants charge that the record does not contain substantial evidence to support this Board conclusion.

This emphasis on similarities or differences in methods of deriving the NAIL DNA misses the main point of this obviousness question. Of note, the record nowhere suggests that the technique in Valiante's Example 12 for isolating NAIL (p38) DNA, even if slightly different than the technique disclosed in the claimed invention, would not yield the same polynucleotide claimed in claim 73. Stated directly, the record shows repeatedly that Valiante's Example 12 produces for any person of ordinary skill in this art the claimed polynucleotide.

More to the point, however, any putative difference in Valiante's/Sambrook's and appellants' *processes* does not directly address the obviousness of representative claim 73, which claims a genus of *polynucleotides*. The difference between Valiante's and the application's techniques might be directly relevant to obviousness in this case if Kubin and Goodwin had claimed a method of DNA cloning or isolation. But they did not. Appellants claim a gene sequence. Accordingly, the obviousness inquiry requires this court to review the Board's decision that the claimed sequence, not appellants' unclaimed cloning technique, is obvious in light of the abundant prior art.

[5] In any event, this court determines that the Board had substantial evidence to conclude that appellants used conventional techniques, as taught in Valiante and Sambrook, to isolate a gene sequence for NAIL. In particular, appellants' arguments that Valiante and Sambrook are deficient because they do not provide "any guidance for the preparation of cell culture that will serve as a useful source of mRNA for the preparation of a cDNA library," Appellants' Br. 34, are diminished by appellants' own disclosure:

> A "nucleotide sequence" refers to a polynucleotide molecule in the form of a separate fragment or as a component of a larger nucleic acid construct. The nucleic acid molecule has been derived from DNA or RNA isolated at least once in substantially pure form and in a quantity or concentration enabling identification, manipulation, and recovery of its component nucleotide sequences by *standard biochemical methods (such as those outlined in Sambrook* et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989)).

'859 Application at 16–17 (emphasis added). Thus, Kubin and Goodwin cannot represent to the public that their claimed gene sequence can be derived and isolated by "standard biochemical methods" discussed in a well-known manual on cloning techniques, while at the same time discounting the relevance of that very manual to the obviousness of their claims. For this reason as well, substantial evidence supports the Board's factual finding that "[a]ppellants employed conventional methods, 'such as those outlined in Sambrook,' to isolate a cDNA encoding NAIL and determine the cDNA's full nucleotide sequence (SEQ NOS: 1 & 3)." *Board Decision* at 5.

In a similar vein, this court reviews the Board's reference to the teachings of Mathew and the connection between Mathew's 2B4 and Valiante's p38 proteins.

As an initial point, the Board referenced Mathew only as cumulative of Sambrook and Valiante. Therefore, the Board's obviousness analysis does not explicitly rely on Mathew at all. Instead the Board observed that Mathew is "exemplary of how routine skill in the art can be utilized to clone and sequence the cDNA of a similar polypeptide." *Id.* In that connection, the record shows that a researcher of ordinary skill in this art would have recognized that both Valiante and Mathew are indisputably focused on regulation of NK cells—Mathew with regard to mice and Valiante with regard to humans. Like Valiante's Example 12, Mathew discusses a detailed protocol for identifying, isolating, and cloning cDNA encoding 2B4, which was later discovered to be the murine equivalent of Valiante's p38 and appellants' NAIL protein. Moreover, Mathew expressly states that his genomic DNA blot analysis "identified a human homologue of the 2B4 gene." Mathew at 5333. In sum, substantial evidence supports the Board's conclusion that Matthew reinforces the relative ease of deriving the claimed sequence following the teachings of the prior art.

[6] This court notes that Matthew contains some data that "suggests that [the] 2B4 gene is not expressed in humans." *Id.* This part of the record, however, does not undermine the Board's correct conclusion that Mathew does not "teach away" from combining its teachings with Valiante. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994). According to Mathew, "[i]t appears ... that the 2B4 gene is somewhat conserved during evolution." Mathew at 5335. Mathew's quasi-agnostic stance toward the existence of a human homologue of the 2B4 gene cannot fairly be seen as dissuading one of ordinary skill in the art from combining Mathew's teachings with those of Valiante. Rather, Mathew's disclosure, in light of Valiante's teachings regarding the p38 protein and its role in NK cell activation, would have aroused a skilled artisan's curiosity to isolate the gene coding for p38. Thus, the record supplies ample evidence to support the Board's finding that Mathew "exemplifies how the cDNA encoding 2B4, the mouse version of Valiante's p38 expressed on all NK cells, can be isolated and sequenced." *Board Decision* at 10.

This court also observes that the Board had no obligation to predicate its obviousness finding on factual findings regarding a prior art teaching of NAIL's binding to the CD48 protein. Even if no prior art of record explicitly discusses the "wherein the polypeptide binds CD48" aspect of claim 73, the Kubin–Goodwin application itself instructs that CD48 binding is not an additional requirement imposed by the claims on the NAIL protein, but rather a property necessarily present in NAIL. *See, e.g.*, '859 Application at 1, 8 (describing CD48 as NAIL's "counterstructure"). Because this court sustains, under substantial evidence review, the Board's finding that Valiante's p38 is the same protein as appellant's NAIL, Valiante's teaching to obtain cDNA encoding p38 also necessarily teaches one to obtain cDNA of NAIL that exhibits the CD48 binding property. *See, e.g., Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249, 66 S.Ct. 81, 90 L.Ed. 43 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect."); *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979) (rejecting the notion that "a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable ... because it also possesses an inherent, but hitherto unknown, function which [paten-

tees] claim to have discovered. This is not the law. A patent on such a structure would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art.").

B.

The instant case also requires this court to consider the Board's application of this court's early assessment of obviousness in the context of classical biotechnological inventions, specifically *In re Deuel*, 51 F.3d 1552 (Fed.Cir.1995). In *Deuel*, this court reversed the Board's conclusion that a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, rendered DNA molecules encoding the protein obvious. *Id.* at 1559. In reversing the Board, this court in *Deuel* held that "knowledge of a protein does not give one a conception of a particular DNA encoding it." *Id.* Further, this court stated that "obvious to try" is an inappropriate test for obviousness.

> *[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious,* in the absence of other prior art that suggests the claimed DNAs.... *"Obvious to try" has long been held not to constitute obviousness.* A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.

Id. (internal citations omitted) (emphases added). Thus, this court must examine *Deuel*'s effect on the Board's conclusion that Valiante's teaching of the NAIL protein, combined with Valiante's/Sam brook's teaching of a method to isolate the gene sequence that codes for NAIL, renders claim 73 obvious.

With regard to *Deuel*, the Board addressed directly its application in this case. In particular, the Board observed that the Supreme Court in *KSR* cast doubts on this court's application of the "obvious to try" doctrine:

> To the extent *Deuel* is considered relevant to this case, we note the Supreme Court recently cast doubt on the viability of *Deuel* to the extent the Federal Circuit rejected an "obvious to try" test. *See KSR Int'l Co. v. Teleflex Inc.*, [550 U.S. 398], 127 S.Ct. 1727, 1737–38, 1740–41 [167 L.Ed.2d 705], 82 U.S.P.Q.2d 1385, 1394, 1396 (2007) (citing *Deuel*, 51 F.3d at 1559). Under *KSR*, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated.

Board Decision at 8. Insofar as *Deuel* implies the obviousness inquiry cannot consider that the combination of the claim's constituent elements was "obvious to try," the Supreme Court in *KSR* unambiguously discredited that holding. In fact, the Supreme Court expressly invoked *Deuel* as a source of the discredited "obvious to try" doctrine. The *KSR* Court reviewed this court's rejection, based on *Deuel*, of evidence showing that a particular combination of prior art elements was obvious because it would have been obvious to one of ordinary skill in the art to attempt such a combination:

> The only declaration offered by KSR—a declaration by its Vice President of Design Engineering, Larry Willemsen—did not go to the ultimate issue of motivation to combine prior art, i.e. whether one of ordinary skill in the art would have been motivated to attach an electronic control to the support bracket of the assembly disclosed by Asano. Mr. Willemsen did state that an electronic control "could have been" mounted on the support bracket of a pedal assembly.

(Willemsen Decl. at P33, 36, 39.) Such testimony is not sufficient to support a finding of obviousness, however. *See, e.g., In re Deuel*, 51 F.3d 1552, 1559 (Fed.Cir.1995) ("'Obvious to try' has long been held not to constitute obviousness.").

Teleflex, Inc. v. KSR Int'l Co., 119 Fed. Appx. 282, 289 (Fed.Cir.2005). The Supreme Court repudiated as "error" the *Deuel* restriction on the ability of a skilled artisan to combine elements within the scope of the prior art:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance *the fact that a combination was obvious to try might show that it was obvious under § 103.*

KSR, 550 U.S. at 421, 127 S.Ct. 1727 (internal citation omitted) (emphasis added).

The Supreme Court's admonition against a formalistic approach to obviousness in this context actually resurrects this court's own wisdom in *In re O'Farrell*, which predates the *Deuel* decision by some seven years. This court in *O'Farrell* cautioned that "obvious to try" is an incantation whose meaning is often misunderstood:

> It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under § 103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under § 103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir.1988). To differentiate between proper and improper applications of "obvious to try," this court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under § 103. In the first class of cases,

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Id. In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness. The inverse of this proposition is succinctly encapsulated by the Supreme Court's statement in *KSR* that where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under § 103 arises. 550 U.S. at 421, 127 S.Ct. 1727.

The second class of *O'Farrell*'s impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d at 903. Again, *KSR* affirmed the logical inverse of this statement by stating

that § 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417, 127 S.Ct. 1727.

This court in *O'Farrell* found the patentee's claims obvious because the Board's rejection of the patentee's claims had not presented either of the two common "obvious to try" pitfalls. Specifically, this court observed that an obviousness finding was appropriate where the prior art "contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." 853 F.2d at 902 (emphasis added). Responding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court stated: "[o]bviousness does not require absolute predictability of success ... *all that is required is a reasonable expectation of success.*" *Id.* at 903–04 (emphasis added). The Supreme Court in *KSR* reinvigorated this perceptive analysis.

KSR and *O'Farrell* directly implicate the instant case. Appellants' claim 73 recites a genus of isolated nucleic acid molecules encoding the NAIL protein. As found by the Board, the Valiante reference discloses the very protein of appellants' interest—"p38" as per Valiante. *Board Decision* at 4. Valiante discloses a monoclonal antibody mAb C1.7 that is specific for p38/NAIL, and further teaches a five-step protocol for cloning nucleic acid molecules encoding p38/NAIL using mAb C1.7. *Id.* In fact, while stating that "[t]he DNA and protein sequences for the receptor p38 may be obtained by resort to conventional methodologies known to one of skill in the art," '690 Patent at col.7 ll.49–51, Valiante cites to the *very same* cloning manual, Sambrook, cited by Kubin and Goodwin for their proposition that the gene sequence is identified and recovered "by standard biochemical methods." '859 Application at 16. Moreover, the record strongly reinforces (and appellants apparently find no room to dispute) the Board's factual finding that one of ordinary skill would have been motivated to isolate NAIL cDNA, given Valiante's teaching that p38 is "expressed by virtually all human NK cells and thus plays a role in the immune response." *Board Decision* at 6. The record shows that the prior art teaches a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific to the protein for cloning this gene. Therefore, the claimed invention is "the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421, 127 S.Ct. 1727. Or stated in the familiar terms of this court's long-standing case law, the record shows that a skilled artisan would have had a resoundingly "reasonable expectation of success" in deriving the claimed invention in light of the teachings of the prior art. *See O'Farrell*, 853 F.2d at 904.

This court also declines to cabin *KSR* to the "predictable arts" (as opposed to the "unpredictable art" of biotechnology). In fact, this record shows that one of skill in this advanced art would find these claimed "results" profoundly "predictable." The record shows the well-known and reliable nature of the cloning and sequencing techniques in the prior art, not to mention the readily knowable and obtainable structure of an identified protein. Therefore this court cannot deem irrelevant the ease and predictability of cloning the gene that codes for that protein. This court cannot, in the face of *KSR*, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art. *See In re Durden*,

763 F.2d 1406, 1411 (Fed.Cir.1985) ("Our function is to apply, in each case, § 103 as written to the facts of disputed issues, not to generalize or make rules for other cases which are unforeseeable."). As this court's predecessor stated in *In re Papesch*, "[t]he problem of 'obviousness' under section 103 in determining the patentability of new and useful chemical compounds ... is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of patent law." 315 F.2d 381, 386 (CCPA 1963).

The record in this case shows that Valiante did not explicitly supply an amino acid sequence for NAIL or a polynucleotide sequence for the NAIL gene. In that sense, Kubin and Goodwin's disclosure represents some minor advance in the art. But "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *KSR*, 550 U.S. at 419, 127 S.Ct. 1727. "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* at 427, 127 S.Ct. 1727. In light of the concrete, specific teachings of Sambrook and Valiante, artisans in this field, as found by the Board in its expertise, had every motivation to seek and every reasonable expectation of success in achieving the sequence of the claimed invention. In that sense, the claimed invention was reasonably expected in light of the prior art and "obvious to try." *See Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008) ("KSR posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness."). These references, which together teach a protein identical to NAIL, a commercially available monoclonal antibody specific for NAIL, and explicit instructions for obtaining the DNA sequence for NAIL, are not analogous to prior art that gives "no direction as to which of many possible choices is likely to be successful" or "only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. As the Board found, the prior art here provides a "reasonable expectation of success" for obtaining a polynucleotide within the scope of claim 73, *Board Decision* at 6, which, "[f]or obviousness under § 103 [is] all that is required." *O'Farrell*, 853 F.2d at 903. Thus, this court affirms the Board's conclusion as to obviousness.

IV.

For the reasons stated above, the Board did not err in finding appellants' claims obvious as a matter of law. Thus, this court need not address appellants' contention that the Board erred in finding its claims invalid under § 112 ¶ 1. Accordingly, this court affirms the decision of the Board.

AFFIRMED.

COSTS

Each party shall bear its own costs.

PALMYRA PACIFIC SEAFOODS, L.L.C., Palmyra Pacific Enterprises, L.L.C., PPE Limited Partnership, and Frank Sorba, Plaintiffs–Appellants,

v.

UNITED STATES, Defendant–Appellee.

No. 2008–5058.

United States Court of Appeals, Federal Circuit.

April 9, 2009.

Background: Commercial fishing entities brought action against the United States

EX PARTE RINKEVICH

Appeal No. 2007-1317

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DEBORA RINKEVICH and JOHN MICHAEL GARRISON

Appeal 2007-1317
Application 09/731,623
Technology Center 2100

Decided: May 29, 2007

Before JAMES D. THOMAS, ANITA PELLMAN GROSS, and ST. JOHN COURTENAY III, *Administrative Patent Judges.*

COURTENAY, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) from the Examiner's rejection of claims 1-6, 8-14, 16-22, and 24. The Examiner has reconsidered and withdrawn the rejection of claims 7, 15, and 23 (Answer 7). The Examiner has also reconsidered and withdrawn the rejection under 35 U.S.C. § 112, first paragraph, of claims 6, 14, and 22 (Answer 3). With

respect to the rejection of dependent claim 11, the Examiner has indicated on page 11 of the Answer that the rejection of claim 11 has been reconsidered and withdrawn. However, on pages 4 and 6 of the Answer we find the Examiner nevertheless maintains a rejection for claim 11 as being unpatentable over Savill in view of Wu. In order to avoid unnecessary delay and expedite the prosecution of this appeal, we will consider claim 11 as standing rejected as set forth on pages 4 and 6 of the Answer. We note that Appellants address the Examiner's rejection of claims 1-24 in the Brief and there is no Reply Brief.

THE INVENTION

The disclosed invention relates generally to data processing systems, and more particularly, to user authentication and access in a data processing system (Specification 1). The disclosed invention provides a system and method for aggregating authenticated identities. A security context created in response to a first user logon is saved in response to a second logon. A composite or aggregate security context is created based on the identity passed in the second logon. Access may then be granted (or denied) based on the current, aggregated security context. Upon logout of the user based on the second identity, the aggregate security context is destroyed, and the security context reverts to the context previously saved. Alternatively, in another embodiment, all security contexts, including those on the stack, may be destroyed (Specification 8).

Independent claim 1 is illustrative:

1. An authentication method comprising the steps of:
generating a first security context in response to a first user authentication;
generating a second security context in response to a second user authentication, wherein said second security context is an aggregate of said first security context and a security context corresponding to an identity in said second user authentication.

THE REFERENCES

The Examiner relies upon the following references as evidence of unpatentability:

Wu US 5,774,551 Jun. 30, 1998

John Savill, "Where can I find a Unix SU (substitute user) like utility?" InstantDoc #15120, Dec. 10, 1999.

THE REJECTION

The following rejection is on appeal before us:

1. Claims 1-6, 8-14, 16-22, and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Savill in view of Wu.

Rather than repeat the arguments of Appellants or the Examiner, we make reference to the Brief and the Answer for the respective details thereof.

OPINION

Only those arguments actually made by Appellants have been considered in this decision. It is our view, after consideration of the record

before us, that the evidence relied upon does not support the Examiner's rejection of the claims on appeal. Accordingly, we reverse.

Independent claim 1

We consider first the Examiner's rejection of independent claim 1 as being unpatentable over Savill in view of Wu.

Appellants argue that Wu's stacking (i.e., aggregation) of authentication services is not done *in response to a second user authentication*, but rather is preexisting and independent of any actual user authentication action (emphasis in original). Appellants further argue that Wu expressly teaches away from a second user authentication, or of performing any action in response to such (missing) second user authentication, by its teaching of a unified single user logon. Appellants conclude that the Examiner has impermissibly relied upon hindsight in formulating the rejection (Br. 9).

The Examiner disagrees. The Examiner argues that Wu's unified login does include the second user authentication because: (a), the first and the second user authentications in the authentication security system, as recited in the claim, *are not limited to human entry* (which is also consistent with the Specification at page 10, paragraph 2 and page 13, paragraph 4), and (b), Wu's unified login invokes multiple logical authentication services and associated security contexts (or credentials) that are dynamically built and aggregated during run-time. The Examiner argues that by using Wu's "stacking" authentication services (col. 6, l. 65), the security contexts are aggregated depending upon which authentications are invoked and what

credentials are created during run-time. Therefore, the Examiner concludes that Wu does not teach away from a second user authentication by its teaching of a unified single user login (Answer 8-9).

With respect to the issue of hindsight, the Examiner asserts that an artisan would have been motivated to modify Savill with the teachings of Wu by virtue of the nature of the problem to be solved. Specifically, the Examiner argues that Wu resolves the problem presented by Savill, i.e., how to avoid the need to log off an existing user account prior to logging on to a new user account (Savill, p. 1, l. 4).

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Furthermore, "'there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness' . . . . [H]owever, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

We begin our analysis by broadly but reasonably construing the recited term "user authentication" in a manner consistent with the Specification (claim 1). *See In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) ("[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification."). When we look to the Specification for *context*, we agree with the Examiner that the claimed first and the second user authentications are not limited to authentication actually performed by human entry (i.e., performed by the user). Indeed, we find the Specification provides broad support for operations that require no action on the part of a human operator:

> Note that the invention may describe terms such as comparing, validating, selecting, identifying, or other terms that could be associated with a human operator. However, for at least a number of the operations described herein which form part of at least one of the embodiments, no action by a human operator is desirable.
> (Specification 10, ll. 10-13).

> In this way an authentication mechanism is implemented which permits a user to selectively authenticate without necessarily giving up already established access. (Note that a user need not refer to a "human" user but may, for example, include a proxy server running under a user's identity.)
> (Specification p. 13, l. 21 - p. 14, l. 1).

We further agree with the Examiner that Wu teaches multiple logical authentication services that are aggregated (i.e., stacked) so as to permit a single unified login to access multiple authentication services, as follows:

> The ability to use multiple different ones of a given account management service is called *"stacking,"* and it is particularly

> useful in conjunction with the *authentication services*. The configuration file 127 allows *multiple authentication services 109* to be *stacked* for *authenticating a user*, and further enables *unified login* to such *stacked authentication services 109* with a *single password*, and *unified logout* with *a single logout command* [emphasis added].
> (Wu, col. 6, l. 63 - col. 7, l. 4).

Nevertheless, we note that Appellants specifically point out that Wu's stacking of authentication services is not done *in response to* a second user authentication (*see* Br. 9). Appellants further argue that Wu's stacking (i.e., aggregation) of authentication services is *preexisting* and independent of any actual user authentication action (*id.*). We find the issue before us presents a close question, given that the broad language of the claim does not require actual human authentication. Thus, we disagree with Appellants' sweeping assertion that Wu's stacking (i.e., aggregation) of authentication services *is independent of any actual user authentication action*, because user action by a *human* is not required when the language of the claim is accorded a broad but reasonable interpretation consistent with the Specification, as discussed *supra* (*see* Br. 9). However, after closely examining the Wu reference in its entirety, we nevertheless find clear support for Appellants' position that Wu's stacking (i.e., aggregation) of authentication services is *preexisting* (i.e., prestored). Specifically, we find Wu discloses that the stacking (i.e., aggregation) of service associations (i.e., authentication services) is stored in configuration file 127:

> Generally, the configuration file 127 stores a set of service associations. Each service association relates one system entry service 107 with one or more selected account management

> services. The selected account management services may be of the same type, or from various types. The service associations form a decision table [*see* TABLE 1, col. 7] used by the pluggable account management interface 123 to determine which account management service is to be used [to] provide account management functionality in response to the use of a particular system entry service 107.
> (Wu, col. 7, ll. 5-14; *see also* TABLE 1, col. 7].

Therefore, we agree with Appellants that Wu's preexisting, stored service associations (i.e., authentication services) are not fairly *generated* (i.e., created) as a second security context *in response to* a second user authentication, wherein said second security context is an aggregate of said first security context and a security context corresponding to an identity in said second user authentication, as required by the language of independent claim 1.

With respect to Appellants' teaching away argument, we agree that Wu's primary purpose of providing a *unified single user login* does teach away from any requirement that a second user authentication be performed by a *human* user (*see* Wu, col. 3, ll. 14-17). At the same time, we agree with the Examiner that a broad but reasonable interpretation of the claim language does not require the user authentication to be performed by an actual human user, as discussed *supra* .

However, we find Appellants' arguments persuasive with respect to the issue of hindsight. The Examiner asserts that the *nature of the problem to be solved* would have led an artisan, having knowledge of Savill, to look to Wu to solve the purported deficiencies of Savill (*see* Answer 9-10). The problem or deficiency that the Examiner raises is the need to avoid logging

out before logging on to another session (*see* Answer 10, ¶ 1). The Examiner asserts that Wu solves this problem (*id.*). When we look to the primary Savill reference, we find the single-page reference teaches a Microsoft Windows super-user (SU) utility that allows a system administrator to temporarily start applications running in the security context of a different account *without having to first close all open applications and log off* (Savill, ¶ 1). Thus, we find the problem proffered by the Examiner is already solved by Savill. We note that the U.S. Supreme Court recently reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. *See also Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474. Nevertheless, in *KSR* the Supreme Court also qualified the issue of hindsight by stating that "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. In the instant case, we conclude that a person of ordinary skill in the art *having common sense* at the time of the invention would not have reasonably looked to Wu to solve a problem already solved by Savill. Therefore, we agree with Appellants that the Examiner has impermissibly used the instant claims as a guide or roadmap in formulating the rejection.

For at least the aforementioned reasons, we agree with Appellants that the Examiner has failed to meet the burden of presenting a prima facie case

of obviousness. Accordingly, we will reverse the Examiner's rejection of independent claim 1 as being unpatentable over Savill in view of Wu.

Because independent claims 9 and 17 recite equivalent limitations, we will also reverse the Examiner's rejection of these claims as being unpatentable over Savill in view of Wu for the same reasons discussed *supra* with respect to claim 1. Because we have reversed the Examiner's rejection of each independent claim, we will not sustain the Examiner's rejection of any dependent claims under appeal. Therefore, we also reverse the Examiner's rejection of dependent claims 2-6, 8, 10-14, 16, 18-22 and 24 as being unpatentable over Savill in view of Wu.

DECISION

In summary, we will not sustain the Examiner's rejection of any claims under appeal. Therefore, the decision of the Examiner rejecting claims 1-6, 8-14, 16-22, and 24 is reversed.

REVERSED

pgc

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REAL PARTY IN INTEREST

The real party in interest in this appeal is Elan Pharma International Limited, which is the assignee of the present application as recorded at Reel/Frame numbers 015165/0833.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 1-95 are pending, with claims 12-13, 27, 32-35, 39, 41-43, and 45-95 withdrawn from consideration. Claims 1-11, 14-26, 28-31, 36-38, 40, and 44 are finally rejected, and are the subject of this appeal. The pending claims are presented in Appendix A of this Brief.

STATUS OF AMENDMENTS

No claim amendments were submitted accompanying the response filed on November 5, 2009. No other amendments or submissions are pending in the application.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 and dependent claims 16-26, 28-31, 36-38, 40 and 44 are to be argued in the brief. The relevant citation to the specification is shown in the parentheses below.

Independent claim 1 reads as follows:

1. A nimesulide composition **{p. 1, ll. 7-8}** comprising:

(a) particles of nimesulide **{p. 1, ll. 7-8}** or a salt thereof **{p. 31, ll. 11-13}**, wherein the particles have an effective average particle size of less than 2000 nm **{p. 1, ll. 7-9; p. 6, ll. 16-18}**; and

(b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles **{p. 6, ll. 15-16}**.

Dependent claim 16 reads as follows:

16. The composition of claim 1, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage **{p. 14, ll. 1-3}**.

Dependent claim 17 reads as follows:

17. The composition of claim 16, wherein the T_{max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage **{p. 14, ll. 13-19}**.

Dependent claim 18 reads as follows:

18. The composition of claim 1, wherein the C_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage **{p. 14, ll. 3-6}**.

Dependent claim 19 reads as follows:

19. The composition of claim 18, wherein the C_{max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage **{p. 14, ll. 20-25}**.

Dependent claim 20 reads as follows:

20. The composition of claim 1, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage **{p. 14, ll. 6-9}**.

Dependent claim 21 reads as follows:

21. The composition of claim 20, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage **{p. 14, l. 26 – p. 15, l. 2}**.

Dependent claim 22 reads as follows:

22. The composition of claim 1 which does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions **{p. 15, ll. 13-20}**.

Dependent claim 23 reads as follows:

23. The composition of claim 22, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3% **{p. 16, ll. 5-10}**.

Dependent claim 24 reads as follows:

24. The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human **{p. 15, ll. 21-23}**.

Dependent claim 25 reads as follows:

25. The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human **{p. 15, ll. 23-25}**.

Dependent claim 26 reads as follows:

26. The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human **{p. 15, ll. 25-26}**.

Dependent claim 28 reads as follows:

28. The composition of claim 1, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size of less than 2000 nm **{p. 17, ll. 7-9}**.

Dependent claim 29 reads as follows:

29. The composition of claim 28, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm **{p. 19, ll. 7-16}**.

Dependent claim 30 reads as follows:

30. The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size of less than 2 microns **{p. 17, ll. 23-25}**.

Dependent claim 31 reads as follows:

31. The composition of claim 30, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm **{p. 19, ll. 7-16}**.

Dependent claim 36 reads as follows:

36. The composition of claim 1, additionally comprising one or more non- nimesulide active agents **{p. 23, ll. 24-26}**.

Dependent claim 37 reads as follows:

37. The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator **{p. 24, l. 29; p. 27, l. 28 – p. 28, l. 1}**.

Dependent claim 38 reads as follows:

38. The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines **{p. 24, ll. 10-29}**.

Dependent claim 40 reads as follows:

40. The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac,

lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac **{p. 26, l. 29 – p. 27, l. 28}**.

Dependent claim 44 reads as follows:

44. The composition of claim 1, which has been sterile filtered **{p. 22, ll. 13-14}**.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejections to be reviewed on appeal are the following:

1. Rejection of claims 1-11, 14-26, 28-31, and 44 under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,552,160 to Liversidge et al. ("Liversidge") in view of U.S. Patent No. 6,017,932 to Singh et al. ("Singh");

2. Rejection of claims 1, 36-38, and 40 under 35 U.S.C. §103(a) for allegedly being obvious over Liversidge in view of Singh, and further in view of The Merck Index 12th ed., Merck & Co. pp. 416-417 (1996) ("Merck").

ARGUMENT

I. Introduction

Appellants note that the Examiner further withdraws claim 12-13 and 27 in the non-final Office Action, which were pending in the first Appeal Brief. Although Appellants disagree with the status of the pending claims, in the spirit of advancing prosecution, Appellants acknowledge the claims as pending but reserve the right to rejoin the withdrawn claims upon allowance of a generic claim.

II. Rejection over Liversidge and Singh

A. Lack of any reason to combine the cited references

According to the Examiner, the primary reference, Liversidge, teaches nanoparticulate non-sterol anti-inflammatory drugs (NSAIDs) but does not expressly teach the active agent of the claimed invention, nimesulide. The Examiner contends that one of ordinary skill in the art would have been motivated to modify Liversidge's composition by incorporating nimesulide as the active agent in view of the teaching of Singh. This is because Liversidge teaches nanoparticulate NSAID compositions having reduced gastric irritation and hastened onset of action (Office Action, the paragraph bridging pages 5 and 6), and because Singh teaches that nimesulide has the same or higher efficacy, better gastric tolerance, and is less ulcerogenic in comparison to other NSAIDs (*id.*, the paragraph bridging pages 7 and 8).

First, there is no reason to solve a problem that has already been solved. *See* the Decision on Appeal, *Ex Parte Rinkevich* (Appeal No. 2007-1317 decided on May 29, 2007). The Board concluded that the Examiner incorrectly asserted that an artisan would have looked to Wu (the secondary reference) to solve the purported deficiencies of Savill (the primary reference) because "a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably looked to Wu to solve a problem already solved by Savill" (the paragraph bridging pages 8 and 9). In the present case, the skilled artisan would not have any

reason, in the absence of the teaching of Appellants' invention, to select nimesulide as the active agent and subject it to Liversidge's particle size reduction process in view of the teaching of Singh. Liversidge teaches improving active agent bioavailability by reducing the active agent particle size. Similarly, Singh teaches a novel and synergistic combination of NSAIDs and Piperine to achieve increased bioavailability. *See* the abstract. The problem of poor bioavailability is already solved by either reference alone.

Moreover, according to Singh, the enhanced bioavailability is observed particularly with the NSAIDs "belonging to the category which exhibits its activity by selectively inhibiting cyclooxygenases-II (COX-II) and/or lipooxygenases" (*id.*). Singh further elaborates regarding the synergistic effects of Piperine and nimesulide at column 5, lines 24-35, reproduced below:

> *The incorporation of Piperine, its metabolites or structural analogues or isomers thereof with NSAIDs particularly Nimesulide or derivatives thereof results in a synergistic composition having unexpected increased bioavailability of NSAIDs particularly Nimesulide and derivatives thereof. Therefore the invention does not involve simple mixing of the components. It is also to be noted that Piperine or has no pharmacological properties but when mixed with NSAIDs particularly Nimesulide or derivatives thereof results in a synergistic effect on said NSAIDs particularly Nimesulide causing enhanced activity and bio-availability thereof.*

The Examiner fails to articulate why one skilled in the art would have any reason to subject nimesulide from Singh to Liversidge's particle size reduction process, particularly in view of Singh's teaching that not all NSAIDs but only a subgroup exhibit synergistic effects in combination with Piperine, and that nimesulide exhibits superior improvement of bioavailability when combined with Piperine. In other words, the Examiner's rationale to select nimesulide and put it in the process of Liversidge (to improve bioavailability) does not support why the skilled artisan would abandon the successful process of Singh to improve bioavailability of nimesulide and adopt the particle size reduction process of Liversidge (without the synergistic effects of piperine).

Furthermore, the Examiner is unclear about how to modify Liversidge's particle size reduction teaching in view of the process requiring the use of Piperine disclosed by Singh. Pursuant to *M.P.E.P.* § 2143.01, the proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference. In this case, the Examiner's proposed modification of nimesulide particle size reduction would render the purpose of Singh unsatisfactory or change the principle of operation of Singh, which involves the synergistic effect of nimesulide and piperine.

Second, the articulated reason to combine the teachings of the cited references is defective. As the Examiner correctly pointed out, Liversidge teaches that reduction of the particle size of an NSAID achieved the effect of reduced gastric irritation following oral administration. However, it does not logically follow that the skilled artisan would select nimesulide from a laundry list of NSAIDs and then formulate nimesulide into a nanoparticulate composition in view of the teaching of Singh.

As the Examiner expressly acknowledged, Singh teaches that nimesulide exhibits ***better gastric tolerance and less ulcerogenic properties*** than other NSAIDs. Therefore, the skilled artisan would be ***less*** motivated to select nimesulide to undergo the expensive and time-consuming particle size reduction process to formulate the drug into a nanoparticulate active agent composition in an attempt to improve the gastric toleration of nimesulide, which is already superior to other NSAIDs. Rather, so informed by Singh, the skilled artisan would select NSAIDs other than nimesulide, which NSAIDs have comparatively poor gastric toleration, to develop into a nanoparticulate active agent composition to cure the problem present in the prior art.

Third, in the absence of any reason to combine the teachings of the cited references, the Examiner at most attempted to propose to try every known NSAID with Liversidge's process to obtain a nanoparticulate active agent composition which is presently claimed. Clearly, nimesulide is not explicitly disclosed by Liversidge, which does list about 40 exemplary

NSAIDs. Thus the Examiner requires Singh for the alleged teaching of nimesulide. However, the Examiner would have never thought to look to Singh for nimesulide without the aid of Appellant's claim as a roadmap.

A suggestion to try each species of the subgenus is explicitly rejected as a proper application of an "obvious to try" rationale in the recent Federal Circuit ruling, excerpted below:

> *To differentiate between proper and improper applications of "obvious to try," this court outlined two classes of situations where* ***"obvious to try" is erroneously equated with obviousness under §103****. In the first class of cases, what would have been "obvious to try" would have been to vary all parameters or* ***try each of numerous possible choices*** *until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.*

In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988)); (emphasis added). *Kubin* further analogizes this rejection rationale with "throw[ing] metaphorical darts at a board filled with combinatorial prior art possibilities" with the aid of hindsight, and therefore, is improper. *Id.*

Fourth, even if there was a reason to select nimesulide from Singh and place it in the process of Liversidge, the resulting combination would not teach each and every limitation of the claimed invention. Liversidge is directed to particles less than 400 nm in size. There is no reason supported by facts that would provide a rationale for a person of ordinary skill in the art to select nimesulide from Singh, place it in the process of Liversidge, and instead of forming particles of a size less than 400 nm, to modify Liversidge and make larger particles, i.e., particles less than 2000 nm as presently claimed.

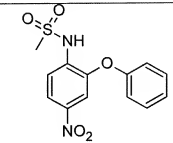
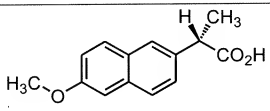
B. Lack of any reasonable expectation of success

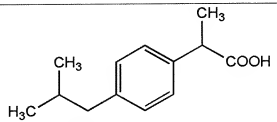
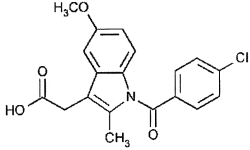
The Examiner is deficient in providing a reasonable expectation of success in obtaining the claimed invention based on a combination of the teachings of Liversidge and Singh. The

Examiner states that "[a] skilled artisan would expect the combination to work, because Singh et al. teaches that nimesulide is poorly soluble and dispersible in at least one liquid medium as required by Liversidge et al." (Office Action, page 9, last full paragraph).

As one skilled in the art would have understood, whether a stable nanoparticulate composition can be obtained for a particular agent depends on many factors, such as the physical and chemical properties of the active agent, the chemical structure of the active agent, the compatibility of the active agent and surface stabilizer, etc. The Examiner fails to establish why the mere fact of poor solubility of nimesulide has any contribution to a reasonable expectation of success.

In fact, nimesulide does not share any structural similarities with the NSAIDs exemplified by Liversidge's working examples to substantiate the Examiner's conclusive statement that a reasonable expectation of success exists. The structure of nimesulide is compared with the NSAIDs exemplified in Liversidge, as detailed in the table below.

NSAID	Structure
nimesulide	
naproxen	

ibuprofen	
indomethacin	

Clearly, nimesulide does not share structural homology with naproxen, ibuprofen, or indomethacin.

"The Federal Circuit has stated that 'rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)." *M.P.E.P.* § 2142. In the absence of any structural similarities, the Examiner has failed to articulate why one skilled in the art would have a reasonable expectation of success by incorporating nimesulide into Liversidge's composition.

C. Independent ground of patentability

(1) Invalid inherency rationale

Dependent claims 16-26 and 28-31 benefit from separate grounds of patentability. The Examiner rejected these claims directed to compositions having specific T_{max}, C_{max}, AUC and redispersion profiles by a simple statement that "the prior art teaches the composition, the properties applicant claims are necessarily present." Office Action at the paragraph bridging

pates 8 and 9. Contrary to the Examiner's conclusory statement, the Examiner has not established that the claimed composition is the same as the prior art.

More specifically, the Examiner asserts that "the compositions of Liversidge et al. as modified by Singh et al. would also be expected to possess the absorption properties recited by claims 22-24 and the redispersal properties recited by claims 28-31." *Id.* Here the Examiner appears to say that "the compositions of Liversidge et al as modified by Singh et al." inherently possess the properties of the claimed composition.

However, this inherency doctrine is applied with self-contradiction because the Examiner's rejection is entirely based on the rationale that combining the teachings of Liversidge and Singh would result in the claimed composition. Therefore, the Examiner's statement is no different than saying that Appellants' claimed composition (the combination of Liversidge and Singh) necessarily possesses the same properties of Appellants' claimed composition.

Accordingly, the rejection should be reversed in whole for lack of a valid basis.

(2) Improper reliance on common knowledge

Without citing to any publications prior to the filing date of the present application, the Examiner asserts that claim 44 is obvious because it is well-known in the medicinal arts that pharmaceutical compositions must be free of biological and chemical contaminants in order to be safe and effective" (Office Action, page 9, 1st full paragraph).

Pursuant to *M.P.E.P.* § 2144.03, "[i]t would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known" (original emphasis).

In the present case, the Examiner has failed to articulate how to sterile-filter a nanoparticulate active agent composition, whether it is obvious to sterile-filter the claimed

composition, or whether it is feasible to sterile-filter the claimed composition by citing any publications. Rather, the Examiner has one overly general statement that "pharmaceutical compositions must be free of biological and chemical contaminants in order to be safe and effective." However, this statement is incomplete and inaccurate. For example, many pharmaceutical compositions formulated in oral dosage forms or in topical dosage forms are not sterile-filtered.

The rejection should be reversed in whole because the Examiner has failed to properly establish a *prima facie* case of obviousness.

III. Rejection over Liversidge, Singh and Tertiary References.

The foregoing discussions concerning Liversidge and Singh are incorporated by reference. The Examiner relies on Merck for the alleged teaching of a non-nimesulide active agent recited in claims 36-38 and 40.

Merck does not remedy the deficiencies of Liversidge and Singh, as discussed *supra*.

Moreover, the Examiner acknowledges that neither Liversidge nor Singh teaches Appellants' claimed composition comprising a non-nimesulide active agent, such as codeine. The Examiner asserts that Singh teaches that nimesulide has analgesic properties and Merck discloses codeine has analgesic properties, and therefore, it is obvious to include codeine in Appellants' claimed composition.

First, the Examiner has failed to explain why one skilled in the art would have included a secondary active agent which is an analgesic in view of Singh's teaching that nimesulide already has analgesic properties.

Second, following the Examiner's rationale, which is fully informed by improper hindsight, one skilled in the art would have included numerous other active agents, as long as they are disclosed in the Merck Index.

Third, claim 37 further prescribes that the secondary active agent may be an analgesic, an anti-inflammatory, an antipyretic, or a vasomodulator. Claims 38 and 40 recite the subgenus and species of the secondary active agents. The Examiner is completely silent as to how one skilled in the art would have included these active agents in addition to nimesulide in Appellants' claimed invention. Therefore, the Examiner has not made a *prima facie* case of obviousness by articulating how these claim limitations are met by the teachings of any cited art, individually or in combination.

Accordingly, Appellants respectfully request that the Board reverse the rejection under 35 U.S.C. §103(a) in whole.

CONCLUSION

For the reasons discussed above, Appellants respectfully submit that all pending claims are in condition for allowance, and respectfully request that the rejections be reversed in whole, and that the claims be allowed to issue.

Respectfully submitted,

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APPENDIX A:

CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A nimesulide composition comprising:

(a) particles of nimesulide or a salt thereof, wherein the particles have an effective average particle size of less than 2000 nm; and

(b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.

2. (Previously Presented) The composition of claim 1, wherein the nimesulide is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

3. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

4. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Original) The composition of claim 1, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

9. (Original) The composition of claim 1, comprising two or more surface stabilizers.

10. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

11. (Original) The composition of claim 10, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate,

carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

12. (Withdrawn) The composition of claim 10, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

13. (Withdrawn) The composition of claim 10, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide,

C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Original) The composition of claim 1, comprising as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

15. (Original) The composition of any of claims 10, 12, or 13, wherein the composition is bioadhesive.

16. (Original) The composition of claim 1, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

17. (Previously Presented) The composition of claim 16, wherein the T_{max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

18. (Original) The composition of claim 1, wherein the C_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

19. (Previously Presented) The composition of claim 18, wherein the C_{max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

20. (Original) The composition of claim 1, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

21. (Previously Presented) The composition of claim 20, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

22. (Previously Presented) The composition of claim 1 which does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions.

23. (Previously Presented) The composition of claim 22, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

24. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

25. (Original) The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

26. (Original) The composition of claim 24, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

27. (Withdrawn) The composition of claim 1, further comprising at least one additional nimesulide composition having an effective average particle size which is different than the effective average particle size of the nimesulide composition of claim 1.

28. (Previously Presented) The composition of claim 1, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size of less than 2000 nm.

29. (Previously Presented) The composition of claim 28, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

30. (Previously Presented) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size of less than 2 microns.

31. (Previously Presented) The composition of claim 30, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

32. (Withdrawn) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than 2000 mPa·s, measured at 20°C, at a shear rate of 0.1 (1/s).

33. (Withdrawn) The composition of claim 32, having a viscosity at a shear rate of 0.1 (1/s) selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

34. (Withdrawn) The composition of claim 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 1/200, less than 1/100, less than 1/50, less than 1/25, and less than 1/10 of the viscosity of a liquid dosage form of conventional non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

35. (Withdrawn) The composition of claims 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 5%, less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%,

less than 85%, and less than 90% of the viscosity of a liquid dosage form of conventional, non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

36. (Original) The composition of claim 1, additionally comprising one or more non-nimesulide active agents.

37. (Previously Presented) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

38. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

39. (Withdrawn) The composition of claim 38, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin,

glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

40. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of aceclofenac, acemetacin, ε-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate,

indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

41. (Withdrawn) The composition of claim 38, in which the vasomodulator is selected from the group consisting of caffeine, theobromine, and theophylline.

42. (Withdrawn) The composition of claim 38, in which the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac,

fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

43. (Withdrawn) The composition of claim 38, in which the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, SC-236, NS-398, SC-58125, SC-57666, SC-558, SC-560, etodolac, DFU, monteleukast, L-745337, L-761066, L-761000, L-748780, DUP-697, PGV 20229, iguratimod, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, flurbiprofen, nabumetone, flosulide, piroxicam, diclofenac, lumiracoxib, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, zomepirac analogs, RS 104894, SC 41930, pranlukast, SB 209670, and APHS

44. (Original) The composition of claim 1, which has been sterile filtered.

45. (Withdrawn) A method of making a nimesulide composition comprising contacting particles of nimesulide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a nimesulide composition having an effective average particle size of less than 2000 nm, wherein the at least one surface stabilizer is adsorbed on the surface of the nimesulide particles.

46. (Withdrawn) The method of claim 45, wherein said contacting comprises grinding.

47. (Withdrawn) The method of claim 46, wherein said grinding comprises wet grinding.

48. (Withdrawn) The method of claim 45, wherein said contacting comprises homogenizing.

49. (Withdrawn) The method of claim 45, wherein said contacting comprises:

(a) dissolving the particles of nimesulide or a salt thereof in a solvent;

(b) adding the resulting nimesulide solution to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized nimesulide having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

50. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

51. (Withdrawn) The method of claim 45, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1000 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

52. (Withdrawn) The method of claim 45, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

53. (Withdrawn) The method of claim 45, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

54. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

55. (Withdrawn) The method of claim 45, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

56. (Withdrawn) The method of claim 45, comprising at two surface stabilizers.

57. (Withdrawn) The method of claim 45, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

58. (Withdrawn) The method of claim 57, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

59. (Withdrawn) The method of claim 57, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

60. (Withdrawn) The method of claim 57, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl

(ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

61. (Withdrawn) The method of claim 45, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

62. (Withdrawn) The method of any of claims 57, 59, or 60, wherein the composition is bioadhesive.

63. (Withdrawn) A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

(a) particles of nimesulide or a salt thereof, wherein the nimesulide particles have an effective average particle size of less than 2000 nm; and

(b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.

64. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

65. (Withdrawn) The method of claim 63, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

66. (Withdrawn) The method of claim 63, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

67. (Withdrawn) The method of claim 63, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

68. (Withdrawn) The method of claim 63, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

69. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

70. (Withdrawn) The method of claim 63, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

71. (Withdrawn) The method of claim 63, comprising at two surface stabilizers.

72. (Withdrawn) The method of claim 63, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

73. (Withdrawn) The method of claim 72, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

74. (Withdrawn) The method of claim 72, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

75. (Withdrawn) The method of claim 72, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl

dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

76. (Withdrawn) The method of claim 63, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

77. (Withdrawn) The method of any of claims 72, 74, or 75, wherein the composition is bioadhesive.

78. (Withdrawn) The method of claim 63, wherein administration of the nimesulide composition does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions, when administered to a human.

79. (Withdrawn) The method of claim 78, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

80. (Withdrawn) The method of claim 63, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

81. (Withdrawn) The method of claim 80, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

82. (Withdrawn) The method of claim 80, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

83. (Withdrawn) The method of claim 63, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

84. (Withdrawn) The method of claim 83, wherein the T_{max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

85. (Withdrawn) The method of claim 63, wherein the C_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

86. (Withdrawn) The method of claim 85, wherein the C_{max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

87. (Withdrawn) The method of claim 63, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

88. (Withdrawn) The method of claim 87, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

89. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents.

90. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents effective for treating fever, inflammation or pain.

91. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

92. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

93. (Withdrawn) The method of claim 63, wherein the subject is a human.

94. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition selected from the group consisting of rheumatic and joint diseases, arthritis, rheumatoid arthritis, osteoarthritis, periarthritis, tendonitis, bursitis, ankylosing spondylitis, joint stiffness, lower back pain, gynecological conditions, menstrual migraine attack, dysmenorrhoea, pelvic inflammatory disease, urological conditions, urethritis, prostatitis, and vesiculitis pyrexia, cardiovascular diseases, atherosclerosis, hypotension, thrombophlebitis, arthrosis; inflammatory conditions, otitis, rhinitis, sinusitis, pharyngitis, bronchitis nephrotoxicity, mastitis, asthma,

cancer, trauma, surgery, migraine headaches, kidney disease, Alzheimer's disease, familial adenomatous polyposis, diarrhea, colonic adenomas bone resorption, and related conditions.

95. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition where anti-inflammatory agents, anti-angiogenesis agents, antitumorigenic agents, immunosuppressive agents, NSAIDs, COX-2 inhibitors, analgesic agents, anti-thrombotic agents, narcotics, or antifebrile agents are typically used.

APPENDIX B:

EVIDENCE

1. U.S. Patent No. 5,552,160 to Liversidge et al.;

2. U.S. Patent No. 6,017,932 to Singh et al.; and

3. The Merck Index 12th ed., Merck & Co. pp. 416-417 (1996).

Appendix B: EVIDENCE

1. US Patent No. 5,552,160

US005552160A

United States Patent [19]

Liversidge et al.

[11] Patent Number: 5,552,160

[45] Date of Patent: *Sep. 3, 1996

[54] SURFACE MODIFIED NSAID NANOPARTICLES

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[73] Assignee: NanoSystems L.L.C., Collegeville, Pa.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,145,684.

[21] Appl. No.: 402,662

[22] Filed: Mar. 13, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 897,193, Jun. 10, 1992, abandoned, which is a continuation-in-part of Ser. No. 647,105, Jan. 25, 1991, Pat. No. 5,145,684.

[51] Int. Cl.[6] A61K 9/14

[52] U.S. Cl. 424/489; 424/450; 424/495; 424/499

[58] Field of Search 424/489, 450, 424/499, 495

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Price et al, Drugs, 40, (Suppl. 5):1–11 (1990) Mechanisms of NSAID-Induced Gastroenteropathy.

Aabakken et al, 65–73, Comparison of the Gastrointestinal Side Effects of Naproxen Formulated as Plain Tablets, Enteric-Coated Tablets, or Enteric-Coated Granules in Capsules.

Gursoy et al "Evaluation of Indomethacin Nanocapsules for their Physical Stability and Inhibitory Activaty on Inflammation and Platelet Aggregation" Chemical Absracts, vol. 111, No. 8, 1989 pp. 101–108.

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Attorney, Agent, or Firm—Rudman & Balogh

[57] ABSTRACT

Dispersible particles consisting essentially of a crystalline NSAID having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm. Pharmaceutical compositions containing the particles exhibit reduced gastric irritation following oral administration and/or hastened onset of action.

13 Claims, No Drawings

SURFACE MODIFIED NSAID NANOPARTICLES

This application is a continuation of U.S. patent application Ser. No. 07/897,193, filed Jun. 10, 1992, now abandoned, which was a continuation-in-part of U.S. patent application Ser. No. 647,105, filed Jan. 25, 1991, now U.S. Pat. No. 5,145,684, issued Sep. 8, 1992.

BACKGROUND OF INVENTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used and therapeutically effective groups of drugs. However, gastric irritation problems constitute the most frequently recognized adverse side effect following oral administration of NSAIDs. Such side effects are well recognized and must be weighed against the clinical efficacy of the drugs.

A great amount of research has been undertaken in an attempt to understand the underlying mechanism responsible for these effects. For example, Cioli et al, *Tox. and Appl. Pharm.*, 50, 283–289 (1979) suggest that gastrointestinal lesions in laboratory animals resulting from the oral administration of acidic NSAIDs may depend on two different mechanisms: a local action exerted by contact with the gastric mucosa and a generalized/centrally mediated (systemic) action, taking place following oral administration.

More recently, Price et al, *Drugs* 40 (Suppl. 5):1–11, 1990, suggest that NSAID-induced gastric damage occurs as a result of NSAID-mediated direct and indirect acidic damage followed almost simultaneously by the deleterious systemic effect of prostaglandin inhibition.

A variety of strategies have been used in the management of NSAID-induced gastric damage. These include: 1) the development and use of NSAIDs with less toxic potential; 2) the reduction or elimination of the agent that actually causes the injury; and 3) the enhancement of the mucosal defense. However, these approaches have not proven entirely successful.

For example, the most effective means of preventing gastric damage, i.e., by eliminating the primary actiological agent is rarely feasible with NSAIDs inasmuch as patients with severe inflammatory disease are rarely able to cease using these drugs. Although selection of less toxic NSAIDs should prove useful, the only practical solution, at present, is to treat the NSAID induced gastric damage. Misoprostol (a methylated prostaglandin E_1) has been approved by the FDA for use in preventing NSAID gastropathy. However, Misoprostol is expensive, must be administered multiple times daily and can cause unacceptable side effects.

Thus it would be highly desirable to provide NSAID formulations that can exhibit a reduction in gastric irritation. Moreover, it would be desirable to provide NSAID formulations exhibiting hastened onset of action.

SUMMARY OF THE INVENTION

We have discovered that pharmaceutical compositions containing surface modified NSAID nanoparticles exhibit reduced gastric irritation following oral administration and/or more rapid onset of action.

More particularly, in accordance with this invention, there are provided particles consisting essentially of an NSAID having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 400 nm.

This invention further provides a pharmaceutical composition comprising the above-described particles and a pharmaceutically acceptable carrier.

In another embodiment of the invention, there is provided a method of treating a mammal comprising administering to the mammal the above-described pharmaceutical composition.

In yet another embodiment of the invention, there is provided a method of preparing the above-described particles comprising the steps of dispersing an NSAID in a liquid dispersion medium and wet grinding the NSAID in the presence of rigid grinding media, wherein the pH of said medium is maintained within the range of from 2 to 6.

In further embodiments of the invention, there are provided methods of reducing gastric irritation and/or hastening the onset of action which include administering the above-described pharmaceutical composition to a mammal.

It is an advantageous feature of this invention that pharmaceutical compositions containing NSAIDs are provided which exhibit reduced gastric irritation following oral administration.

It is another advantageous feature of this invention that pharmaceutical compositions are provided exhibiting hastened onset of action.

Other advantageous features will become readily apparent upon reference to the following description of preferred embodiments.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is based partly on the discovery that surface modified nanoparticles comprising an NSAID, e.g., naproxen, demonstrate reduced gastric irritation and/or a more rapid onset of action following oral administration. While the invention is described herein primarily in connection with its preferred class of drugs, i.e., NSAIDs, it is also useful in conjunction with other classes of drug substances, e.g., antibiotics, quinolones, antilipemics and roentgenographics.

The particles of this invention comprise an NSAID. The NSAID exists as a discrete, crystalline phase. The crystalline phase differs from an amorphous or non-crystalline phase which results from conventional solvent precipitation techniques, such as described in U.S. Pat. No. 4,826,689. The NSAID can be present in one or more suitable crystalline phases.

The invention can be practiced with a wide variety of NSAIDs. However, the NSAID must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble" it is meant that the NSAID has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably of less than about 1 mg/ml at processing temperature, e.g., room temperature. The preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which the NSAID is poorly soluble and dispersible including, for example, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

The NSAIDs useful in the practice of this invention can be selected from suitable acidic and nonacidic compounds.

Suitable acidic compounds include carboxylic acids and enolic acids. Suitable nonacidic compounds include, for example, nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine and dapsone.

Suitable carboxylic acid NSAIDs include, for example, salicylic acids and esters thereof, such as aspirin, phenylacetic acids such as diclofenac, alclofenac and fenclofenac, and carbo- and heterocyclic acetic acids such as etodolac, indomethacin, sulindac, tolmetin, fentiazac and tilomisole; propionic acids, such as carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen; and fenamic acids, such as flufenamic, mefenamic, meclofenamic and niflumic.

Suitable enolic acid NSAIDs include, for example, pyrazolones such as oxyphenbutazone, phenylbutazone, apazone and feprazone, and oxicams such as piroxicam, sudoxicam, isoxicam and tenoxicam.

The above-described NSAIDs are known compounds and can be prepared by techniques known in the art.

In particularly preferred embodiments of the invention, the NSAID is naproxen, indomethacin or ibuprofen.

The particles of this invention contain an NSAID as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the NSAID but do not chemically bond to the NSAID.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens™, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxomers, such as Pluronic™ F68 and F108, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF, dextran, lecithin, Aerosol OT™, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol™ P, which is a sodium lauryl sulfate, available from DuPont, Triton™ X200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 20 and Tween 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Specialty Chemicals, Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., Crodesta SL-40, which is available from Croda, Inc., and SA90HCO, which is $C_{18}H_{37}$-$CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$. Surface modifiers which have been found to be particularly useful include polyvinylpyrrolidone, Pluronic F-68, and lecithin.

The surface modifier is adsorbed on the surface of the NSAID in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the NSAID or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 400 nm" it is meant that at least 90% of the particles have a number average particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments of the invention, the effective average particle size is less than about 300 nm. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size of less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 400 nm.

The particles of this invention can be prepared in a method comprising the steps of dispersing an NSAID in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the NSAID to an effective average particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The NSAID selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse NSAID selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the NSAID is greater than about 100 μm, then it is preferred that the particles of the NSAID be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse NSAID selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the NSAID in the liquid medium can vary from about 0.1–60%, and preferably is from 5–30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably is 1–75%, more preferably 20–60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the

dispersion to less than 400 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the NSAID and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the NSAID conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. However, zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. Further, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 2.5 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the NSAID. Processing temperatures of less than about 30°–40° C. are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

Milling must be carried out under acidic conditions, at a pH of from 2–6, preferably 3–5. The preferred pH depends, e.g., on the acidity and solubility of the particular NSAID selected. Acid resistant milling equipment is highly preferred, e.g., equipment fabricated of high grade stainless steel, e.g., grade 316 SS, or equipment coated with an acid resistant coating.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20–80 kHz for a time of about 1 to 120 seconds.

The relative amount of the NSAID and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular NSAID and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the NSAID, etc. The surface modifier preferably is present in an amount of about 0.1–10 mg per square meter surface area of the NSAID. The surface modifier can be present in an amount of 0.1–90%, preferably 0.5–80%, and more preferably 1–60% by weight based on the total weight of the dry particle.

A simple screening process has been developed whereby compatible surface modifiers and NSAIDs can be selected which provide stable dispersions of the desired particles. First, coarse particles of an NSAID are dispersed in a liquid in which the NSAID is essentially insoluble, e.g., water at 5% (w/v) and milled for 120 hours in a roller mill under the following milling conditions:

Grinding vessel: 8 oz. (250 ml) glass jar

Available volume of grinding vessel: 250 ml

Media volume: 120 ml

Media type: 1.0 mm pre-cleaned zirconium oxide beads (distributed by Zircoa, Inc.)

Milling time: 120 hours

Slurry volume: 60 ml

RPM: 92

Room Temperature pH: 4.0 (adjusted with HCl or NaOH, if necessary)

The slurry is separated from the milling media by conventional means, e.g., by pouring the slurry out of the vessel, or by using a pipette. The separated slurry is then divided into aliquots and surface modifiers are added at a concentration of between 2 and 50% by weight based on the total combined weight of the NSAID and surface modifier. The dispersions are then sonicated (1 minute, 20 kHz) or vortexed using a multitubed vortexer for one minute, to disperse agglomerates and subjected to particle size analysis, e.g., by photon correlation spectroscopy and/or by examination under an optical microscope (1000× magnification). If a stable dispersion is observed, then the process for preparing the particular NSAID surface modifier combination can be optimized in accordance with the teachings above. By stable it is meant that the dispersion exhibits no flocculation or particle agglomeration visible to the naked eye and, preferably, when viewed under the optical microscope at 1000×, at least 15 minutes, and preferably, at least two days or longer after preparation. In addition, preferred particles exhibit no flocculation or agglomeration when dispersed in 0.1N HCl or simulated GI fluid (USP).

The resulting dispersion is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified NSAID nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral admin-

istration in solid or liquid form, for rectal administration, and the like. A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition. The selected dosage level of the NSAID for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore, depends upon the particular NSAID, the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

It is a particularly advantageous feature that the pharmaceutical compositions of this invention exhibit reduced gastric irritation and/or more rapid onset of action as illustrated in the examples that follow.

The following examples further illustrate the invention.

Example 1

A nanoparticulate naproxen dispersion (Formula 1) was prepared in a roller mill as follows. A 250 ml glass jar was charged with 120 ml of 1.0 mm pre-cleaned Zirconium oxide beads (Zirbeads XR, available from Zircoa Inc., having a nominal diameter of 1.0 mm), 60 g of an aqueous slurry containing 3 g naproxen (5% by weight), purchased from Sigma, St. Louis, Mo., particle size 20–30 μm, and 1.8 g (3% by weight) Pluronic F-68, purchased from BASF Fine Chemicals, Inc., as the surface modifier. The beads were pre-cleaned by rinsing in 1N H_2SO_4 overnight followed by several rinses with deionized water. The batch was rolled at 92 RPM for a total of 120 hours. The dispersion was stable when a portion was added to 0.1N HCl. The average particle size measured by photon correlation spectroscopy was 240–300 nm.

A control formulation of naproxen was prepared by adding 5% (w/v) unmilled naproxen to 3% Pluronic F-68. The suspension was vortexed and sized. The particle size range was 20–30 μm.

The concentration of naproxen in both formulations was 50 mg/mL (w/v). Both formulations were diluted with 3% Pluronic F-68 to a dosing concentration of 10 mg/mL for oral administration.

Male Sprague-Dawley rats were maintained in accordance with the conditions set forth in "Guide for the Care and Use of Laboratory Animals", NIH Publication 86-23 The temperature was maintained at 22±1° C. and the relative humidity was 50±10%, with a 12 hour light/dark cycle. Rats were provided laboratory chow and water. The rats (250–350 g) were anesthetized with a 55 mg/kg intraperitonal injection of Nembutal (sodium pentobarbital). The external Jugular veins were chronically canmulated to facilitate removal of blood samples. Prior to administration of naproxen, the rats were allowed to recover for 24 hours with water ad libtiam.

The rats were anesthetized, with Metofane, orally gavaged with the above-described formulations and placed in a restraint device. Blood samples (100 μl) were obtained via the jugular vein at 0 (pre-administration), 5, 10, 15, 30, 45, 60, 75, 90, 120, 180 and 240 minutes following administration of naproxen and collected in heparinized tubes. Plasma (50 μl) was obtained immediately and placed on ice. Plasma samples (50 μl) were mixed with 130 μl of acetonitrile and 20 μl of a standard solution (20 μg/ml indomethacin) and vortexed to precipitate protein. Samples were centrifuged and the supernatants removed, placed in vials, and analyzed by HPLC. The Separation of naproxen was carried out on an analytical column (Waters Novapak C18; 15 cmx4 mm, 5μ).

At the end of the experiment (240 min.) the rats were euthanized by an I.V. bolus injection of Nembutal via the jugular vein. The stomachs were removed and cut along the line of greater curvature from the duodenum to the pyloric sphincter. The stomachs were then spread flat and pinned out on dissecting dishes, and washed with 0.9% NaCl.

The evaluation and counting of stomach irritations (erosion/lesion/ulcer) were conducted by a modification of arbitrary scoring systems (Cioli et al, *Tox. and Appl. Pharm.*, 1979, 50:283–289 and Beck et al, *Arch. Toxicol.*, 1990; 64: 210–217) correcting for various degrees of severity as noted below. Differences in severity index have been associated with the gastropathology present on the stomach following oral administration of NSAIDs (Balaa, *Am. Journ. Med. Sci.*, 1991, 301:272–276 and Lanza et al; *Dig. Dis. and Sci.*, 1990; 35:12).

Each stomach irritation was measured in length (or diameter) using a 10 mm surgical ruler. The length of the irritations ranged from 0.25 mm to 10.0 mm. Irritations less than 0.25 mm were classified as pinpoint. The irritations were categorized by color as an evaluation of severity. Irritations red in appearance were rated as mild and assigned a severity value of 1. Brown irritations were rated as moderately severe and assigned a value of 2. Irritations which appeared black were rated as the most severe and given a severity value of 3. A score for each irritation was determined by multiplying the length value and the point severity level. The sum total for all irritations on a given stomach was identified as the total irritation score.

Table 1 shows the mean values for the stomach irritations induced by naproxen in the Control formulation and Formulation 1 of this invention. As indicated by the data, the formulation of this invention exhibited a reduction in stomach irritation scores compared to the control ($p=0.099$). It was concluded that the formulation of this invention exhibits reduced gastric irritation following oral administration as compared to the control.

TABLE 1

Rat No.	Control (n = 6)	Formulation 1 (n = 8)
1	293	43
2	200	139
3	133	149
4	140	80
5	110	129
6	101	163
7		54
8		98
Mean	163	107
SEM	30	16

Surprisingly, the formulation of this invention when administered orally induced a similar level of gastric irritation compared to the same formulation administered parenterally, i.e., I.V. Thus, the formulation of this invention appears virtually devoid of a direct irritant effect on the stomach of a rat.

A statistical comparison of the pharmacokinetic plasma parameters Cmax (peak plasma concentration), Tmax (time to peak plasma concentration) and relative bioavailability ($AUC_{0-240\ min}$—from Area Under the Curve values from 0–240 minutes) for Formulation 1 of this invention and the control calculated by the trapezoidal method is set forth below.

	Mean ± SEM	
	Control	Formulation 1
Cmax (μg/ml)	126 ± 4 (n = 5)	187 ± 19 (n = 6)
Tmax (min)	34 ± 3 (n = 5)	24 ± 5 (n = 6)
$AUC_{(0-240\ min)}$ (μg × min/ml)	15,226 ± 994 (n = 5)	19,062 ± 573 (n = 3)

The data indicate that the time to peak plasma concentration were lower for the formulation of this invention compared to the control (p=0.15) and both the relative bioavailability and peak plasma concentrations were significantly higher for the formulation of this invention compared to the control (p=0.03) and (p=0.02), respectively. The increase in apparent rate of absorption clearly suggests enhanced onset of action.

Example 2

The preparation of Example 1 was repeated except that 5% by weight polyvinylpyrrolidone was used in place of the Pluronic F-68. The average particle size was 250 mm.

Examples 3–8 illustrate the preparation of nanoparticulate ibuprofen.

Example 3

Nanoparticulate ibuprofen was prepared in a planetary mill (Pulverisette-7, manufactured by Fritsch, Gmbh) containing two 25 ml bowls. The initial charge (per bowl) included 12.5 ml of 1 mm pre-cleaned zirconium oxide beads and 6.25 ml of an aqueous slurry containing 100 mM HCl, 3% (w/v) ibuprofen, and 2% (w/v) Pluronic F-68 as the surface modifier. The ibuprofen formulation was milled for 24 hours at 325 RPM. The resulting dispersion was stable when a portion was added to simulated gastric fluid, i.e., 2 g NaCl, 3.2 g pepsin, 7 ml HCl, and H_2O to 1 liter, pH=1.2. The average particle size measured by photon correlation spectroscopy was 253 nm.

Example 4

Example 3 was repeated except that the initial charge included 1% Tween 20 and the milling time was 17 hours. The average particle size was 263 nm.

Example 5

Example 3 was repeated except that the milling time was 4 hours. The average particle size was 314 nm.

Example 6

Example 3 was repeated except that the surface modifier in the initial charge was 1% (w/v) of a 1:2 by weight mixture of Tween 20 and Span 20, and the milling time was 20 hours at 175 RPM. The average particle size was 294 nm.

Example 7

Example 3 was repeated except that the initial charge included 0.25% (w/v) tyloxapol as the surface modifier and 10 mM HCl. The charge was milled for 20 hours at 175 RPM in a refrigerated (5° C.) area. The average particle size was 344 nm.

Example 8

Example 7 was repeated except that Tween 20 was used in place of the tyloxapol. The average particle size was 351 nm.

Examples 9–12 illustrate the preparation of nanoparticulate indomethacin.

Example 9

Nanoparticulate indomethacin was prepared in a roller mill as follows. A 250 ml bottle was charged with 125 ml of 1.0 mm pre-cleaned ZrO_2 beads, 200 gm of an aqueous slurry containing 10 gms indomethacin (5% by weight) and 2 gms Vinol 205, a polyvinylalcohol (1% by weight). A batch size of 200 gms was used to reduce air space in the bottle to minimize the formation of foam. The batch was rolled at 88.5 RPM for a total of 240 hours. The dispersion was stable in 0.1N HCl and simulated gastric fluid as described in Example 3 above. The average particle size measured by photon correlation spectroscopy was 331 nm.

Example 10

Example 9 was repeated except that polyvinylpyrrolidone was used in place of the polyvinylalcohol. The average particle size was 216 nm.

Example 11

Example 9 was repeated except that Pluronic F-68 was used in place of the polyvinylalcohol. The average particle size was 228 nm.

Example 12

Example 9 was repeated except that Pluronic F-108 was used in place of the polyvinylalcohol. The average particle size was 235 nm.

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

1. Particles consisting essentially of 99.9–10% by weight of crystalline NSAID having a solubility in water of less than 10 mg/ml, said NSAID having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an average particle size of less than about 400 nm.

2. The particles of claim 1 having an effective average particle size of less than 300 nm.

3. The particles of claim 1 wherein said surface modifier is present in an amount of 0.5 to 80% by weight based on the total weight of the dry particle.

4. The particles of claim 1 wherein said NSAID is selected from nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone and feprazone, piroxicam, sudoxicam, isoxicam and tenoxicam.

5. The particles of claim 1 wherein said NSAID is selected from naproxen, indomethacin and ibuprofen.

6. The particles of claim 1 wherein said surface modifier

is selected from polyvinylpyrrolidone and a block copolymer of ethylene oxide and propylene oxide.

7. Particles according to claim 1 consisting of naproxen having a block copolymer of ethylene oxide and propylene oxide adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 400 nm.

8. Particles according to claim 1 consisting essentially of naproxen having polyvinylpyrrolidone adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 400 nm.

9. A pharmaceutical composition comprising the particles of claim 1 and a pharmaceutically acceptable carrier.

10. A method of treating a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 9.

11. A method of reducing gastric irritation following oral administration to a mammal of a pharmaceutical composition comprising an NSAID, said method comprising administering the pharmaceutical composition of claim 9.

12. A method of hastening onset of action following administration to a mammal of a pharmaceutical composition an NSAID, said method comprising administering the pharmaceutical composition of claim 9.

13. A method of hastening onset of action following administration to a mammal of pharmaceutical composition, said method comprising administering said pharmaceutical composition in the form of particles consisting essentially of 99.9–10% by weight of a crystalline drug substance having a solubility in water of less than 10 mg/ml, said drug substance having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an average particle size of less than about 400 nm.

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Appendix B: EVIDENCE

2. US Patent No. 6,017,932

US006017932A

United States Patent [19]

Singh et al.

[11] Patent Number: 6,017,932

[45] Date of Patent: Jan. 25, 2000

[54] **PHARMACEUTICAL COMPOSITIONS CONTAINING AT LEAST ONE NSAID HAVING INCREASED BIOAVAILABILITY**

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[21] Appl. No.: **08/988,211**

[22] Filed: **Dec. 10, 1997**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[7] **A61K 31/445**; A61K 31/415; A61K 31/18

[52] **U.S. Cl.** **514/321**; 514/327; 514/330; 514/406; 514/605; 514/682

[58] **Field of Search** 514/321, 327, 514/330, 605, 682, 406

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Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

A novel composition for increasing the bioavailability of Non-steroidal Anti-inflammatory Drugs (NSAIDs), particularly those belonging to the category which exhibits its activity by selectively inhibiting cyclooxygenases-II (COX-II) and/or lipooxygenases, is disclosed. The composition is characterized in having clinically significant increased bioavailability when compared to the known compositions of the drugs. The pharmaceutical compositions comprise NSAIDs and Piperine, as herein disclosed. Enhanced bioavailability of NSAIDs results in the reduction of both dosages and dose-related side effects.

11 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS CONTAINING AT LEAST ONE NSAID HAVING INCREASED BIOAVAILABILITY

BACKGROUND OF THE INVENTION

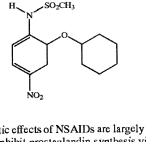
The present invention relates to a novel composition for increasing the bioavailability of Non-steroidal Anti-inflammatory Drugs (NSAIDs) or derivatives thereof particularly those belonging to the category which exhibits its activity by selectively inhibiting cyclooxygenases-II (COX-II) and/or lipooxygenases . More preferably invention related to the drugs like Nimesulide, Nabumetone, Tepoxalin and Flosulide and/or derivatives thereof. The novel composition is characterised in having clinically significant increased bio-availability when compared to the known compositions of the drugs. More particularly the invention relates to a pharmaceutical composition containing NSAIDs such as Nimesulide, Nabumetone, Tepoxalin and Flosulide and/or derivatives thereof and Piperine, its metabolites, structural analogues or isomers of Piperine. The invention also encompasses Kits that may be used in the method of this invention. The Kits would contain one or more doses of NSAIDs and one or more doses of Piperine, its metabolites, structural analogues or isomers of Piperine.

Enhanced bio-availability results in the reduction of the dose of NSAIDs or derivatives thereof and hence will reduce the cost of therapy in diseases like arthritis which require long term therapies which results from the high cost of the drugs. Also as the cost of therapy will decrease, NSAIDs such as Nimesulide can be put to much wider use in newer indications. Enhanced bio-availability of NSAIDs results in the reduction of dose-related side effects.

DESCRIPTION OF THE PRIOR ART

The anti-inflammatory mechanism of NSAIDs is due to reduction in prostaglandin synthesis by the direct inhibition of cyclo-oxygenase (COX). COX exists in two forms—COX-I and COX-II (Wallace J L, Cirino G. The development of gastrointestinal sparing NSAIDs. *Trend Pharmacol Sci.*, 1994, 15, 405–406.). COX-I is found in most tissues and is involved in the physiological production of prostaglandins (PGs) (Masferrer J L, Zweifel B S, Manning P T et.al. Selective inhibition of inducible COX-II in vivo is anti-inflammatory and non-ulcerogenic. *Proc Natl Acad Sci USA.*, 1994, 91, 3228–3232). Inhibition of beneficial PG's in organs such as stomach and kidney can result in gastric lesions, nephrotoxicity and internal bleeding. On the other hand COX-II is cytokine-inducible and is expressed only in inflammatory cells (Masferrer J L, Zweifel B S, Manning P T et.al. Selective inhibition of inducible COX-II in vivo is anti-inflammatory and nonulcerogenic. *Proc Natl Acad Sci USA.*, 1994, 91, 3228–3232). The identification and seperation of constitutive (COX-I) and inducible (COX-II) enzymes have led to development of newer NSAIDs which selectively inhibit the detrimental COX-II and not the beneficial COX-I enzyme. Examples of these newer NSAIDs are Nimesulide, Flosulide and Nabumetone (Insel Pa., Analgesic-Antipyretic and anti-inflammatory agents. In Goodman and Gilmans "The Pharmacological Basis of Therapeutics" Hardman J G, Limbird L E (eds) McGraw-Hill, New York., 617pp). These drugs are being developed as non-ulcerogenic, GIT-sparing, anti-inflammatory agents. Nimesulide is a NSAID that also has antipyretic and analgesic properties. The compound is weakly acidic (pKa=6.5) and differs from other NSAIDs in that its chemical structure contains a sulfonanilide moeity as the acidic group. (Magni E. Nimesulide an overview. Drug Invest 1991;3 Suppl. 2:1–3).

Chemically Nimesulide is N-(4-nitro, 2-phenoxyphenyl) methanesulfonamide, with the following chemical structure:



The therapeutic effects of NSAIDs are largely the result of their ability to inhibit prostaglandin synthesis via inhibition of cyclo-oxygenase. Unfortunately, this effect is also responsible for the inhibition of gastroprotective prostaglandins, which leads to gastrointestinal intolerance. In vitro, Nimesulide is a relatively weak inhibitor of prostaglandin synthesis and appears to exert its effects through a variety of mechanisms. (Magni E. The effect of nimesulide on prostanoid formation. Drugs 1993; 46 Suppl. 1:10–4) Indeed, the mechanism of action of this drug is more complex than previously thought and may involve interference with the production/action of mediators other than prostaglandins such as enzymes, toxic oxygen derivatives, cytokines, platelet-activating factor (PAF) and histamine.

Nimesulide is a novel non steroidal anti-inflammatory drug with better gastric tolerance than other commonly used NSAIDs. It acts mainly through selective COX II inhibition though additional mechanisms of action has been postulated. It has been found to be highly efficacous in cancer pain etc and is comparable or superior to other NSAIDs like diclofenac or piroxicam in different pain models or models of inflammation.

Nimesulide has been given through oral and rectal route and its pharmacokinctic studies in case of these routes have been well documented. Our research group has demonstrated the use of Nimesulide through transdermal and Injectable formulation. (European patent application No. 96304460.7 and 96304461.5 and U.S. patent application Ser. No. 08/662,704 and 08/662,477 respectively).

The anti-inflammatory, analgesic and antipyretic activities of Nimesulide, a (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats.

The analgesic potency of Nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

Nimesulide is a relatively week inhibitor of prostaglandin synthesis in vitro and appears to exert its effects on histamine release, the neutrophil myeloperoxidase pathway, bradykinin activity, tumour necrosis factor-a release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor. Animal studies have suggested that nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen. Nime-

sulide appears to have little effect on renal prostaglandin synthesis in rats.

After oral administration of nimesulide 50 to 200 mg to healthy adult volunteers, peak serum concentrations of 1.98 to 9.85 mg/L are achieved within 1.22 to 3.17 hours. Compared with values obtained with oral drug administration, peak serum concentrations are slightly lower (2.14 to 2.32 mg/L) and are achieved more slowly (3 to 4.58 h) after rectal administration of nimesulide 100 and 200 mg. Oral drug absorption is nearly complete and concomitant administration of food may decrease the rate, but not the extent, of absorption of nimesulide. The drug is extensively bound (99%) to plasma proteins and has an estimated apparent volume of distribution of 0.19 to 0.35 L/Kg following oral administration.

Nimesulide is extensively metabolized (1 to 3% of dose is excreted unchanged in the urine) to several metabolites which are excreated mainly in the urine (~70%) or the feces (~20%). The drug is almost completely biotransformed into 4-hydroxy-nimesulide in both free and conjugated forms and this metabolite appears to contribute to the anti-inflammatory activity of the compound. Peak concentrations of 4-hydroxy-nimesulide ranged from 0.84 to 3.03 mg/L and were attained within 2.61 to 5.33 hours after oral administration of nimesulide 50 to 200 mg to healthy adult volunteers. The elimination half-life of 4-hydroxy-nimesulide ranges from 2.89 to 4.75 hours and is generally similar to or slightly higher than that of the parent compound (1.56 to 4.95 h).

The pharmacokinetic profile of nimesulide is not significantly altered in children, elderly volunteers and patients with moderately impaired renal function [creatinine clearance 1.8 to 4.8 L/h (30 to 80 ml/min]. Slight accumulation of 4-hydroxy-nimesulide was noted in patients with moderate renal impairment; however, the clinical significance of this finding is unknown.

Clinical studies have established the analgesic, anti-inflammatory and antipyretic effectiveness of orally (mostly 200 mg/day) or rectally (400 mg/day) administered nimesulide in the treatment of a variety of painful inflammatory conditions, including those associated with osteoarthritis, oncology, postoperative trauma, sports injuries, ear, nose and throat disorders, dental surgery, bursitis/tendinitis, thrombophlebitis, upper airways inflammation and gynecological disorders. In these indications, nimesulide is more effective than placebo and is at least as effective as therapeutic dosages of other NSAIDs, including: piroxicam, ketoprofen, naproxen, etodolac, mefenamic acid, diclofenac, influmic acid, fentiazac, feprazone and flurbiprofen. Nimesulide therapy was characterised by a rapid onset of analgesia and symptomatic relief in studies where a significant difference in clinical efficacy between active treatments was observed.

Various attempts to improve the solubility and hence the bio-availability of Nimesulide have been reported. Pirotte Bernard et. al (WO 95/34533) have reported the formation of water soluble L-Lysine salt of Nimesulide. The salt was further complexed with Cyclodextrins. The more soluble form can be used to make dosage forms where solubilization is required. More soluble form is contemplated to have better bio-availability from solid dosage forms.

In U.S. Pat. No. 5,283,261 Filippo. Drago has reported the use of Dimethyl Sulphoxide to solubilize Nimesulide in treatment of Cataract. The approach is limited to used in topical or occular drug delivery.

Many workers have reported enhanced solubility and bio-availability of nimesulide hy formation of inclusion compounds with various Cyclodextrins by Co-milling, Kneading or spray-drying techniques, e.g.,

Au Pat No. 7866591

FR Pat No. 2662360

Wo Pat No. 91/17774

Wo Pat No. 9428031

Chang, S F et. al. (Abstract No. 74 from proceedings of the Academy of Pharmaceutical Sciences. Atlanta Ga. 1975b) have reported a comparison between bio-availability of non-micronized and micronized tablets in dogs and human volunteers. Their findings showed significantly greater AUC values (approx 2 fold) and higher peak plasma concentrations with the micronized formulation.

The literature survey revealed that use of certain herbs, e.g., Piper longum and Piper nigrum as adjuncts in Indian System of medicine date back to 6th century Ad and 3rd century BC (Charaka, et al, Charak Samhita, 3rd edn, Nirnaya Sagar Press Bombay, 1991 (in Sanskrit), Kaviraj, K. B. Sushruta Samhita, 2nd ed., Chowk hamba Sanskrit Series, vol. 3, Varanasi, India 1953; Vagbmai, Ashtang Hridaya, Chowkhamba Sanskrit Series, Varanasi, India, 1962 (in Sanskrit).

Bose (Bose K. G. Pharmacopoeia Indica, Bose Laboratories, Calcutta, India 1928) makes a positive mention of the property of long pepper for increasing efficacy of Vasaka as antiasthmatic.

In an attempt to study scientific use of above herbs a research group (Usha Zutshi and J. L. Koul, Indian Drugs, 19 (12), 476479, 1982), observed the effect of Trikatu (a composition comprising of Piper nigrum, Piper longum & Zingiber officinalis in equal proportion w/w) as a whole on vasicine resulting in enhanced bioavailability (and therefore the activity) of this drug to a great extent. Piper longum and Piper nigrum both are almost equally effective, whereas ginger (Zingiber officinalis) alone has no significant such enhancing effect.

In a recent art U.S. Pat. No. 5,439,891 the active constituent of Piper longum and Piper nigrum, Piperine, was shown to increase bio-availability of certain anti-tubercular and anti-leprosy drugs like Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Dapsone. The analysis of pharmacokinetic data shows that the mean increase in AUC for Rifampicin was 37.6%, Isoniazid was 131%, & Pyrazinamide was 36% when the formulations contained Piperine as a part of composition when compared with those which did not contain Piperine. The invention described in U.S. Pat. No. 5,439,891 is limited to demonstration of scope of use of Piperine as bio-availability enhancer in therapy of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Dapsone only. It has been specifically referred to in this study that the synergistic activity of Piperine ou drugs is not uniform and appears to be selective. This was based on the inventors finding that Piperine has no effect on enhancing the bio-availability of synthetic antidiahetic drugs such as tolbutamide.

U.S. Pat. No. 5,439,891 does indicate that Piperine may be useful as a bioavailability enhancer in drugs Rifampicin, Pyrazinamide, Isoniazid, Ethambutol and Dapsone. All these are low molecular weight drugs and none of these drugs have poor bioavailabilty like the one exhibited by NSAIDS particularly Nimesulide.

EPO application no. 94116731.4 and publication no. EP 0 709 098 A1 in the Patel, Modi et.al describes use of Piperine as bio-availability enhancer for several broad categories of drugs. There is also mention of Non-steroidal Anti-inflammatory drugs. However this EP application has not tested the utility of Piperine in the new classes of NSAIDs

such as those disclosed in the present invention. Its is surprising that Patel, Modi et.al reported the human volunteer data in the European Application without any previous publication or reference of the animal data of such experiments. On critical examination of the specification the inventors also opine that the number of drugs for which increase in bio-availability has been reported appears to be unjustified in view of the human effort and time required for such experiments.

SUMMARY OF THE INVENTION

In accordance with present invention there is disclosed a composition of Piperine, its metabolites, structural analogues or isomers thereof along with atleast one NSAIDs which enhances the bio-availibilty of NSAIDs derivatives thereof.

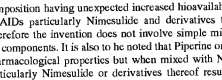
DETAILED DESCRIPTION OF THE INVENTION

The incorporation of Piperine, its metabolites or structural analogues or isomers thereof with NSAIDs particularly Nimesulide or derivatives thereof results in a synergistic composition having unexpected increased bioavailability of NSAIDs particularly Nimesulide and derivatives thereof. Therefore the invention does not involve simple mixing of the components. It is also to be noted that Piperine or has no pharmacological properties but when mixed with NSAIDs particularly Nimesulide or derivatives thereof results in a synergistic effect on said NSIADs particularly Nimesulide causing enhanced activity and bio-availibilty thereof.

Piperine, (E, E) 1-[5-(1,3-benzodioxyl-5-yl)-1-oxo-2,4-pentadenyl] piperidine is the main constituent of many Piper species. It is mostly obtained from Piper longum (3–5%) or Piper nigrum (3–9%) which are cultivated commercially.

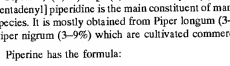
Piperine has the formula:

(1)

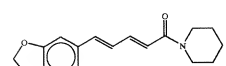


Examples of its metabolites are as follows:

(2)



(3)



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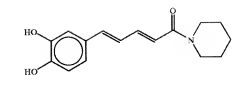
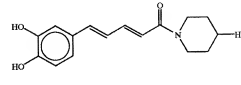
(4)



(5)



Piperine as a parent molecule and/or one or more of its metabolites and/or analogues thereof may have a role in enhancing bio-availability of drugs. Examples of Piperine analogues are derivatives in which the piperidine ring is substituted, e.g. by an amino group, or esters (e.g. C_{1-6} alkyl esters) of metabolites containing an OH group.

Piperine forms monoclimic prisms from ethanol mp 130° C. It is tasteless at first but induces a burning sensation after a few seconds. It is neutral to litmus (pKa 12.22). It is soluble in benzene, chloroform, ether, ethyl acetate, dichloromethanc, alcohol, acetic acid and insoluble in water, pet. ether.

On alkaline hydrolysis it furnishes a base piperidine and the acid viz. piperic acid, mp 216° C. It may be synthesized by condensing the two components under proper conditions.

It has the following spectral characteristics:

UV (methanol): max 340 mu (32,000).

IR(KBr): 1633, 1610, 1580, 1510, 1440, 1250, 1190, 1130, 1030, 995, 930, 842 cm^{-1}.

Piperine is commercially available. In addition, Piperine can be isolated from oleo-resin of Piper nigrum (Black pepper) or Piper longum (Long pepper). The powdered fruits of the plant (Piper nigrum) are extracted with dichloromethanc at room temperature with stirring for 12 hours. The extract is filtered, concentrated in vacuum and the residue is subjected to purification on an alumina column. Pure Piperine can be obtained either from petroleum ether/ethyl acetate fractions or dichloromethanc to give crude Piperine. Pure Piperine can be obtained by crystallization from ethanol. Piperine can also be obtained directly from the crude residue in lesser amounts by extraction in alcohol, filtration and successive crystallisation. Piperine metabolites, analogues and isomers can be prepared synthetically.

Preferably NSAIDs such as Nimesulide is present in the composition from 0.1 mg/kg body wt. to 6.0 mg/kg body Vt. and Piperine is 0.01 mg/kg body wt. to 10.0 mg/kg body wt.

Prefcably Nabumetone is present in the composition from 0.1 mg/kg body wt. to 50.0 mg/kg body wt. and Piperine is 0.01 mg/kg body wt. to 10.0 mg/kg body wt.

EXPERIMENT I

To demonstrate the effect of the novel composition, an experiment was conducted employing the composition containing Nimesulide with Piperine in a pre-determined dose on rats. The results of the experiment are illustrated in Table-1. It was found during administration of the composition of tbe invention on the experimental animals that increase in bio-availability will result in the reduction of dose and bence cost of therapy in long term diseases like arthritis. Also a reduction in dose related side-effects can be anticipated.

In order to prove the effect of Piperine on bio-availability of Nimesulide from its composition, albino rats of either sex of body weight 200 g±10 gms were taken. The rats were housed 5 per cage with food and water provided ad libidum.

On the day of experimentation the rats were randomised into ten batches of 5 rats each. Four groups were formed. Group I consisted of one batch of 5 rats, which was kept as control which received no drug treatment. Group II consisted of four batches of five rats each. This group was administered with Composition containing Nimesulide alone, at a dose level of 1.8 mg/Kg body wt, in the form of suspension of micronised drug in distilled water. Rats of batch 1 from Group II were sacrificed 60 minutes post treatment after Chloroform anaesthesia. Batch 2,3 and 4 were similarly sacrificed at 120 min., 240 min. and 360 min. post treatment respectively. Blood was collected from the rats from the ventricle into heparinised tubes.

Group III consisted of one batch of 5 rats, which received only Piperine at a dose level of 1.0 mg/kg body wt. The animals were sacrificed 160 minutes post treatment after Chloroform anaesthesia. Blood was collected from the rats from the ventricle into heparinised tubes.

Group IV consisted of 4 batches of 5 rats each. This group was administered with composition containing Nimesulide at a dose level 1.8 mg/kg body wt. and Piperine at a dose level 1.0 mg/kg body wt., in the form of suspension of micronised drugs in distilled water. Rats of batch 1 from Group IV were sacrificed 60 minutes post treatment after Chloroform anaesthesia. Batch 2, 3 and 4 were similarly sacrificed at 120 min., 240 min. and 360 min. post treatment respectively. Blood was collected from the rats from the ventricle into heparinised tubes.

The blood samples were centrifuged at 3700 rpm and the plasma separated. To 1 ml plasma 0.5 ml of HCl was added and then extracted with 2 ml of benzene. Extracted benzene was evaporated in a water bath at 95° C. and reconstituted with 100 μl of mobile phase and 10 μl was injected into the HPLC.

Waters HPLC fitted with C_8 μ Bondapack was used along with Waters UV-Vis detector (254 nm). Acetonitrile 50% with 50% Ammonium di-hydrogen Phosphate (0.01M) in double distilled, filtered (0.22 μ) water was used as the mobile phase.

The retention time for Nimesulide was 4.26 min. Unpaired student T test was applied on the data. Level of significance was fixed at p<0.05.

In the animals of Group I no peak corresponding to retention time of Nimesulide was seen. In the animals of Group II where composition containing Nimesulide alone was administered, the drug could be detected by 60 minutes of administration. The plasma levels reached at this point of time is 5.8±1.7 (S.D.) mg/ml of plasma. Statistically significant levels (P<0.05) were attained at 120 min. post treatment with drug concentration in plasma being 7.9±2.3 mg/ml. Concentration of the drug, at 240 min and 360 min. was 4.6±1.4 kg/ml and 2.2±1.1 mg/ml, respectively.

The present study demonstrates that significant amount of Nimesulide reaches the systemic circulation by 60 min. of administration of composition containing Nimesulide alone through the oral route and the drug levels can be seen till 360 min. post treatment. The study also demonstrates that when the composition containing Nimesulide alongwith Piperine is administered, the average plasma levels are 43% higher at 60 min, 95% higher at 120 min., 113% higher at 240 min. and 272% higher at 360 min. post treatment than the plasma levels obtained after administration of composition containing Nimesulide alone.

The data in provided herein above illustrates explicitly the inventors' findings that the addition of Piperine to Nimesulide enhances the bio-availability of Nimesulide significantly.

TABLE I

	Plasma levels of Nimesulide (mg/ml) Post treatment time			
Group	60 min.	120 min.	240 min.	360 min.
Group I	—	—	—	—
Group II	5.8 ± 1.7	7.9 ± 2.3	4.6 ± 1.4	2.2 ± 1.1
Group III	—	Nil	—	—
Group IV	8.3 ± 2.2	15.4 ± 3.3	9.8 ± 2.8	6.0 ± 1.9

EXPERIMENT II

In another set of experiments in mice, Nimesulide was administered alone and in combination with Piperine at sub-threshold dose level and compared with threshold level for the analgesic activity monitored be acetic acid induced writhing technique. Pharmacokinetic studies were also performed in rats. The aim of the experiments was to see whether Nimesulide when administered at low dosage level alongwith Piperine could produce significant pharmacological response or not.

The study design for acetic acid induced writhing in mice was as follows:

TABLE II

GROUP No.	TREATMENT REGIME
I.	Vehicle treated (distilled water + gum acacia) - no drug
II.	Nimesulide (6.5 mg/kg)
III.	Nimesulide (10 mg/kg)
IV.	Nimesulide (10 mg/kg) + Piperine (1 mg/kg)
V.	Nimesulide (10 mg/kg) + Piperine (3 mg/kg)
VI.	Nimesulide (10 mg/kg) + Piperine (5 mg/kg)
VII.	Nimesulide (10 mg/kg) + Piperine (10 mg/kg)
VIII.	Nimesulide (6.5 mg/kg) + Piperine (10 mg/kg)

The single test point pharmacokinetic studies were performed in two groups of rats. Group I received Nimesulide only at a dose of 10 mg/kg administered orally. Group II received Nimesulide (10 m/kg) with Piperine (10 mg/kg) administered orally. Rats were sacrificed at 90 minutes. post treatment and blood samples were analysed by HPLC.

The results of the acetic acid induced writhing produced very surprising results. Whereas Nimesulide above 6.5 mg/kg dose failed to show any analgesic activity; when administered alongwith Piperine produced significant analgesia.

The results of the experiment are given below

TABLE III

PROTECTION AGAINST ACETIC ACID INDUCED WRITHING GROUPS (n = 8)		
GROUP No.	TREATMENT REGIME	% PROTECTION
I.	Vehicle treated (distilled water + gum acacia)	0%
II.	Nimesulide (6.5 mg/kg)	17%
III.	Nimesulide (10 mg/kg)	54%

TABLE III-continued

PROTECTION AGAINST ACETIC ACID INDUCED WRITHING GROUPS (n = 8)

GROUP No.	TREATMENT REGIME	% PROTECTION
IV.	Nimesulide (10 mg/kg) + Piperine (1 mg/kg)	56%
V.	Nimesulide (10 mg/kg) + Piperine (3 mg/kg)	72%**
VI.	Nimesulide (10 mg/kg) + Piperine (5 mg/kg)	76%**
VII.	Nimesulide (10 mg/kg) + Piperine (10 mg/kg)	87%***
VIII.	Nimesulide (6.5 mg/kg) + Piperine (10 mg/kg)	55%#

***= p < 0.001, **= p < 0.01; (#= p < 0.01 comparing Group VIII with Group II)

The results of pharmacokinetic studies corroborated the fact that Piperine causes increased bioavailability of Nimesulide. The Plasma concentrations of Nimesulide when administered with Piperine were higher than when Nimesulide was administered alone and this correlate well with the therapeutic analgesic action of the composition.

TABLE IV

Pharmacokinetic study in Rats

	Groups	
	Nimesulide + Piperine	Nimesulide
Number of animals	5	5
Dosage	10 mg/kg + 10 mg/kg	10 mg/kg
Plasma concentration (90 min post treatment)	11.485 mg/ml*	8.818 mg/ml

The invention will now be described with reference to the following examples.

Example - I

DIFFERENT COMPOSITIONS FOR TEPOXALIN AND PIPERINE CAPSULES

Composition	1	2	3
Tepoxalin	25 mg	50 mg	100 mg
Piperine	2 mg	5 mg	10 mg
Lactose	205 mg	179 mg	187 mg
Magnesium Stearate	8 mg	8 mg	8 mg
Sodium Lauryl Sulphate	2 mg	3 mg	5 mg
Total	242 mg	245 mg	310 mg

Example - II

DIFFERENT COMPOSITIONS FOR NABUMETONE TABLETS

Composition	1	2	3
Nabumetone	1000 mg	50 mg	1500 mg
Piperine	100 mg	5 mg	150 mg
Starch	97 mg	150 mg	110 mg
Microcrystalline Cellulose	100 mg	114 mg	115 mg
Polyvinyl Pyrrolidone	18 mg	5.0 mg	30 mg
Magnesium Stearate	15 mg	3.0 mg	20 mg
Purified Talc	20 mg	3.0 mg	25.0 mg
Total	1350 mg	330 mg	1950 mg

Example III -

DIFFERENT COMPOSITIONS FOR KIT CONTAINING NIMESULIDE AND PIPERINE TABLETS.

Component 1		
Nimesulide	—	100 mg
Starch	—	80 mg
Microcrystalline Cellulose	—	120 mg
Polyvinyl Pyrrolidone	—	4.0 mg
Magnesium Stearate	—	3.0 mg
Purified Talc.	—	3.0 mg
Colloidal Silicon Dioxide	—	5.0 mg
Total	—	315 mg
Component 2		
Piperine	—	10 mg
Starch	—	63 mg
Dicalcium Phosphate	—	40 mg
Polyvinyl Pyrrolidone	—	2.0 mg

-continued

Magnesium Stearate	—		2.0 mg
Purified Talc	—		3.0 mg
Total	—		120 mg

Example - IV
DIFFERENT COMPOSITIONS FOR NIMESULIDE WITH PIPERINE TABLETS

Composition	1	2	3	4	5	6	7	8
Nimesulide	5 mg	25 mg	100 mg	100 mg	150 mg	200 mg	300 mg	400 mg
Piperine	1 mg	5 mg	100 mg	1 mg	50 mg	50 mg	100 mg	25 mg
Starch	160 mg	135 mg	35 mg	100 mg	35 mg	85 mg	65 mg	41 mg
Microcrystalline cellulose	80 mg	80 mg	40 mg	74 mg	35 mg	35 mg	100 mg	100 mg
Dicalcium Phosphate	64 mg	65 mg	43 mg	43 mg	36 mg	36 mg	—	—
Purified Talc	5.0 mg	5.0 mg	5.0 mg	5.0 mg	6.0 mg	6.0 mg	6.0 mg	6.0 mg
Magnesium Stearate	3.0 mg	3.0 mg	4.0 mg	4.0 mg	4.0 mg	4.0 mg	8.0 mg	8.0 mg
Colloidal Silicon Dioxide	3.0 mg	3.0 mg	3.0 mg	3.0 mg	3.0 mg	3.0 mg	6.0 mg	8.0 mg
Povidone	4.0 mg	4.0 mg	5.0 mg	5.0 mg	6.0 mg	6.0 mg	15.0 mg	12.0 mg
Total	325 mg	325 mg	335 mg	335 mg	325 mg	425 mg	600 mg	600 mg

Example - V
DIFFERENT COMPOSITIONS FOR NIMESULIDE WITH PIPERINE CAPSULES

Nimesulide	100 mg	50 mg	150 mg	200 mg	250 mg	300 mg	300 mg	400 mg
Piperine	10 mg	25 mg	75 mg	40 mg	100 mg	5 mg	50 mg	50 mg
Lactose	140 mg	160 mg	57 mg	54 mg	150 mg	140 mg	125 mg	100 mg
Colloidal Silicon Dioxide	5 mg	5 mg	8 mg	8 mg	8 mg	10 mg	5 mg	5 mg
Purified Talc	5 mg	5 mg	10 mg	8 mg	12 mg	10 mg	10 mg	10 mg
Total	260 mg	245 mg	300 mg	310 mg	520 mg	465 mg	490 mg	565 mg

Example - IV
DIFFERENT COMPOSITIONS FOR NIMESULIDE WITH PIPERINE TABLETS (COATED)

Composition	1	2	3	4	5	6	7	8	9
Nimesulide	100 mg	100 mg	150 mg	50 mg	25 mg	200 mg	300 mg	400 mg	25 mg
Piperine	20 mg	40 mg	20 mg	40 mg	75 mg	100 mg	10 mg	50 mg	1 mg
Starch	80 mg	100 mg	70 mg	90 mg	80 mg	75 mg	75 mg	100 mg	80 mg
Dicalcium Phosphate	100 mg	60 mg	100 mg	80 mg	110 mg	120 mg	70 mg	100 mg	40 mg
Povidone	6 mg	8 mg	10 mg	6 mg	8 mg	10 mg	10 mg	10 mg	12 mg
Magnesium Stearate	10 mg	10 mg	10 mg	8 mg	10 mg	8 mg	10 mg	10 mg	12 mg
Purified Talc	10 mg	10 mg	8 mg	9 mg	12 mg	8 mg	12 mg	12 mg	12 mg
Hydroxypropyl Methyl Cellulose	15 mg	20 mg	15 mg	25 mg	30 mg	25 mg	50 mg	40 mg	60 mg
Polyethylene Glycol - 400	3 mg	4 mg	4.0 mg	3.0 mg	4.0 mg	4 mg	5 mg	8 mg	12 mg
*Isopropyl alcohol *Methylene Chloride Titanium Dioxide	6 mg	8 mg	13 mg	14 mg	14 mg	10 mg	8 mg	10 mg	11 mg
Total	350 mg	380 mg	400.0 mg	325.0 mg	325.0 mg	560 mg	550 mg	740 mg	255 mg

* Lost during processing

Example - VII
DIFFERENT COMPOSITIONS OF NIMESULIDE WITH PIPERINE SUSPENSION

Composition	1	2	3	4	5	6
Nimesulide	1.0% w/v	2.0% w/v	0.5	3.0% w/v	4.0% w/v	4.0% w/v
Piperine	0.1% w/v	0.2% w/v	0.02	0.5% w/v	10% w/v	0.2% w/v
Xanthan Gum	0.3% w/v	0.35% w/v	0.3%	0.3% w/v	0.3% w/v	0.25% w/v
Glycerol	10.0% w/v	15.0% w/v	10.0%	12.0% w/v	15.0% w/v	18.0% w/v
Cremophore RH-40	1.0% w/v	1.0% w/v	0.75% w/v	10.25	1.25% w/v	1.25% w/v
Sorbitol Solution	30% w/v	35% w/v	30% w/v	45% w/v	50% w/v	40% w/v
Colloidal silicon dioxide	0.25% w/v	0.25% w/v	0.2% w/v	0.25% w/v	0.3% w/v	0.3% w/v
Methyl Paraben Sodium	0.18% w/v	0.18% w/v	0.15% w/v	0.2% w/v	0.2% w/v	0.2% w/v
Propyl paraben sodium	0.1% w/v	0.1% w/v	0.01% w/v	0.1% w/v	0.1% w/v	0.09% w/v
Citric Acid	3.0% w/v	3.0% w/v	3.0% w/v	3.0% w/v	3.0% w/v	3.2% w/v
Flavour Mango	0.15% w/v	0.15% w/v	0.1% w/v	0.2% w/v	0.2% w/v	0.2% w/v
Colour Quinoline yellow	q.s	q.s	q.s	q.s	q.s	q.s
Purified Water	q.s to 100%	q.s. to 100%	q.s to 100%	q.s to 100%	q.s to 100%	q.s to 100%

The examples of formulation given above should not be construed to limit the scope of the invention. In fact following these examples, any suitable or desired Pharmaceutical formulation containing a NSAID particularly Nimesulide can be prepared.

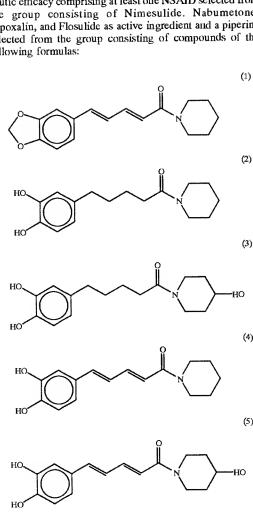
The composition of the invention can be in any form commonly employed for administration i.e. drink solution, a concentrated drink solution to be diluted before use, solution encapsulated in soft gelatin capsules, solution adsorbed on suitable adsorbents leading to formulations such as tablets,

capsules and granules, the solution freeze dried for oral, topical solution or Injectable dosage forms and the like.

The composition according to this invention can be formulated to be administered topically, orally, rectally, vaginally, parenterally, by inhalation or by any other conventional method of administration. Also any other pharmaceutical form(s) known to the persons qualified in the art e.g. effervescent tablets, fast dissolving products, sustained release/controlled release/zero-order release products and alike can be construed. Another embodiment of this invention is a kit which comprises one or more pharmaceutically acceptable doses of NSAIDs or derivatives thereof or a mixture thereof and one or more pharmaceutical doses of Piperine, its metabolites, structural analogues, isomers thereof or a mixture thereof.

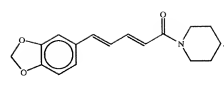
We claim:

1. A pharmaceutical composition having increased therapeutic efficacy comprising at least one NSAID selected from the group consisting of Nimesulide, Nabumetone, Tepoxalin, and Flosulide as active ingredient and a piperine selected from the group consisting of compounds of the following formulas:



and derivatives thereof where the piperidine ring is amino-substituted; and derivatives thereof where the OH groups are replaced by C_{1-6} alkyl esters.

2. A composition as claimed in claim 1 comprising an NSAID and piperine having the formula



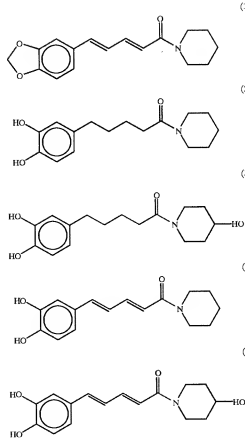
3. A composition according to claim 1, wherein the NSAID comprises Nimesulide.

4. A pharmaceutical composition as claimed in claim 1 in the form of a liquid preparation, tablet, capsule or granule.

5. A pharmaceutical composition as claimed in claim 1 in the form of a suspension of the active ingredients.

6. A pharmaceutical composition as claimed in claim 1 wherein the NSAID is present in an amount ranging from 0.1–50 mg/Kg body weight and the piperine is present in an amount ranging from 0.01–10 mg/Kg body weight.

7. A kit comprising one or more pharmaceutically acceptable doses of an NSAID selected from the group consisting of Nimesulide, Nabumetone, Tepoxalin and Flosulide and one or more pharmaceutically acceptable doses of a piperine selected from the group consisting of compounds of the following formulas:



derivatives thereof where the piperidine ring is amino-substituted; and derivatives thereof where the OH groups are replaced by C_{1-6} alkyl esters.

8. A kit according to claim 7, wherein the NSAID comprises Nimesulide.

9. A kit as in claim **7** wherein the pharmaceutically acceptable doses are in the form of a liquid preparation, tablet, capsule or granule.

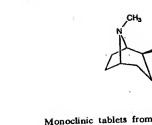
10. A kit as claimed in claim **7** wherein the pharmaceutically acceptable doses are in the form of a suspension of the active ingredients.

11. A kit as claimed in claim **7** wherein the NSAID is present in an amount ranging from 0.1–50 mg/Kg body weight and the piperine is present in an amount ranging from 0.01–10 mg/Kg body weight.

* * * * *

Appendix B: EVIDENCE

3. Merck Index 12th Ed., Merck & Co. pp. 416-417 (1996)



Monoclinic tablets from alcohol, mp 98°. Volatile, esp above 90°, but the sublimate is not crystalline. bp_{40} 187-188°. $[\alpha]^{20}_{D}$ −35° (50% alcohol); $[\alpha]^{20}_{D}$ −16° (c = 4 in chloroform). Aq solns are alkaline to litmus. pKa (15°) 8.61. pKb (15°) 5.59. One gram dissolves in 600 ml water, 270 ml water at 80°, 6.5 ml alcohol, 0.7 ml chloroform, 3.5 ml ether, 12 ml oil turpentine, 12 ml olive oil, 30-50 ml liquid petrolatum. Also sol in acetone, ethyl acetate, carbon disulfide. LD_{50} i.v. in rats: 17.5 mg/kg (Rose).

Hydrochloride. $C_{19}H_{23}NO_4$·HCl, *cocaine muriate.* Crystals, granules, or powder; saline, slightly bitter taste; numbs tongue and lips. mp ~195°. $[\alpha]_D$ −72° (c = 2 in aq soln pH 4.5). One gram dissolves in 0.4 ml water; 3.2 ml cold, 2 ml hot alcohol; 12.5 ml chloroform. Also sol in glycerol, acetone. Insol in ether or oils. Avoid heat in preparing soln as it decomposes. Preserve in well-closed, light-resistant containers.

Nitrate dihydrate. $C_{19}H_{23}N_5O_{13}$·2H_2O, crystals, mp 58-63°. Freely sol in water or alcohol; slightly sol in ether.

Sulfate. $C_{17}H_{21}NO_4·H_2SO_4$, white, granular, crystalline powder. Sol in water or alcohol.

Caution: May be habit forming. Cocaine and its derivatives are controlled substances listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1995).

THERAP CAT: Anesthetic (local).
THERAP CAT (VET): Topical anesthetic (ophthalmic).

2518. Cocculus. Fish-berry; Indian berry; *Cocculus indicus;* oriental berry. Dried fruit of *Anamirta cocculus* (L.) Wight & Arn., *Menispermaceae. Habit.* East Indies, Malay Archipelago. *Constit.* Menispermine, paramenispermine, about 1% picrotoxin, picrotoxic acid, cocculine alkaloid, about 50% fat. *Poisonous!*

THERAP CAT: CNS and respiratory stimulant.

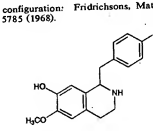
2519. Cochineal. The dried female insect, *Coccus cacti* L., enclosing the young larvae. *Habit.* Mexico, Central America; cultivated in West Indies, Canary Islands, Algiers, and Southern Spain. About 70,000 insects to 1 lb. *Constit.* About 10% carminic acid, about 2% coccerin (a wax), about 10% fat. The coloring matter—alkali carminate—is contained only in the fatty parts of the insect and in the yolk of the eggs, to the extent of 10-14%.

USE: Coloring food products and toilet preparations; the source of carmine and carminic acid for manuf red and pink inks and lakes.

2520. Cocillana. Dried bark of *Guarea rusbyi* (Britt.) Rusby, *Meliaceae. Habit.* Bolivia. *Constit.* Rusbyine, about 2.5% resins, about 2.5% fat, tannin.

THERAP CAT: Expectorant.
THERAP CAT (VET): Has been used as an expectorant.

2521. Coclaurine. *(S)-1,2,3,4-Tetrahydro-1-[(4-hydroxyphenyl)methyl]-6-methoxy-7-isoquinolinol;* 1-(*p*-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline; machiline. $C_{17}H_{19}NO_3$ mol wt 285.34. C 71.56%, H 6.71%, N 4.91%, O 16.82%. Isolated as the racemate from species of *Machilus (Lauraceae)* and *Cocculus (Menispermaceae).* First isoln from *C. laurifolius* D.C. believed to be of the *d*-form: Kondo, Kondo, *J. Pharm. Soc. Japan* no. 524, 876 (1925), *C.A. 20,* 604² (1926); *see also* Johns *et al., Aust. J. Chem.* 20, 1729 (1967). Structure: Kondo, Kondo, *J. Pharm. Soc. Japan* 48, 1156 (1928); Tomita, Kusuda, *Ibid.* 72, 280 (1952). Synthesis: Kratz, Billek, *Monatsh.* 82, 568 (1951); Finkelstein, *J. Am. Chem. Soc.* 73, 550 (1951). Identity with machiline: Tomita *et al., J. Pharm. Soc. Japan* 83, 218 (1963), *C.A.* 59, 2874a (1963). Crystal structure and absolute configuration: Fridrichsons, Mathieson, *Tetrahedron* 24, 5785 (1968).



Plates, tablets from alc, mp 220-221°. Sol in hot alc, hot acetone; slightly sol in water, alc, chloroform, ether, acetone; practically insol in benzene, petr ether.

Hydrochloride. $C_{17}H_{19}NO_3$·HCl, crystals, mp 263-264°.

2522. Cocoa. A powder prepd from the roasted and cured kernels of ripe seeds of *Theobroma cacao* L. and other species of *Theobroma, Sterculiaceae.* For bibliography *see* Cacao Shell.

Brownish powder of chocolate odor and taste.

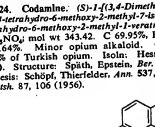
USE: In nutrient beverages; as flavoring.

2523. Coconut Oil. Copra oil. Expressed oil from kernels of *Cocos nucifera* L., *Palmae. Constit.* Trimyristin, trilaurin, tripalmitin, tristearin; also various other glycerides.

White, semisolid, lard-like fat; stable to air. Remains bland and edible for several years under ordinary storage conditions. d^{40}_{4} 0.903. mp 21-25°. n^{40}_{D} 1.4485-1.4495. Sap. no. 255-258. Iodine no. 8-9.5. Acid no. not over 6. Surface tension (20°): 33.4 dyn/cm; (80°): 28.4 dyn/cm. Practically insol in water, 95% alc, more sol in abs alc; very sol in chloroform, ether, carbon disulfide. Soly data: Rao, Arnold, *J. Am. Oil Chem. Soc.* 33, 389 (1956).

USE: Manuf soap, edible fats, chocolate, candies; in baking instead of lard; in candles and night lights; in dyeing cotton; as an ointment base; in hair dressing; in massage.

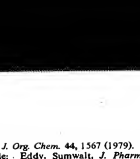
2524. Codamine. *(S)-1-[(3,4-Dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolinol; 1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-veratryl-7-isoquinolinol. 4-tetrahydro-6-methoxy-2-methyl-1-veratryl-7-isoquinolinol.* $C_{20}H_{25}NO_4$ mol wt 343.42. C 69.95%, H 7.34%, N 4.08%, O 18.64%. Minor opium alkaloid. Constituutes about 0.003% of Turkish opium. Isoln: Hesse, *Ann.* 282, 213 (1894). Structure: Späth, Epstein, *Ber.* 59B, 2791 (1926). Synthesis: Schöpf, Thierfelder, *Ann.* 537, 143 (1939); Billek, *Monatsh.* 87, 106 (1956).



dl-Form, large, six-sided prisms from ether, mp 127°. Very sol in alcohol, chloroform. Somewhat sol in boiling water. In soln codamine reacts strongly basic. The salts are bitter in taste, whereas the base is said to be tasteless.

2525. Codeine. *(5a,6a)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol;* methylmorphine; morphine monomethyl ether; morphine 3-methyl ether; Codicept. $C_{18}H_{21}NO_3$ mol wt 299.37. C 72.22%, H 7.07%, N 4.68%, O 16.03%. Present in opium from 0.7 to 2.5%, depending on the source, but mostly prepd by methylation of morphine. *q.v.* Discussion of structure and bibliography: Small, Lutz, "Chemistry of the Opium Alkaloids," *U.S.* Small, Lutz, "Chemistry of the Opium Alkaloids," *U.S. Public Health Reports,* Suppl. No. 103, Washington (1932). Prepn of (+)-codeine and racemate: Goto, Yamammoto, *Proc. Japan Acad.* 30, 769 (1954), *C.A.* 50, 1052b (1956); of (−)-form: E. J. Bijsterveld, H. J. Sinnige, *Rec. Trav. Chim.* 95, 24 (1976); H. C. Beyerman *et al., ibid.* 97, 127 (1978). Manuf from morphine: W. R. Heumann, *Bulletin an Narcotics* X, 15 (1958). Facile synthesis from thebaine, *q.v.*: W.

G. Dauben *et al., J. Org. Chem.* **44,** 1567 (1979). Toxicity of the hydrochloride: Eddy, Sumwalt, *J. Pharmacol. Exp. Ther.* **67,** 127 (1939). Comprehensive description of codeine and codeine phosphate, q.v.: F. J. Mubtadi, M. M. A. Hassan, *Anal. Profiles Drug Subs.* **10,** 93-138 (1981).



Monohydrate, orthorhombic sphenoidal rods or tablets (octahedra) from water or dil alcohol, mp 154-156° (after drying at 80°). Sublimes (when anhydr) at 140-145° under 1.5 mm pressure. Melts to oily drops when heated in an amount of water insufficient for complete soln, crystallizes on cooling. d_4^{20} 1.32. $[\alpha]_D^{25}$ −136° (c = 2 in alcohol), $[\alpha]_D^{25}$ −112° (c = 2 in chloroform). pK (15°) 6.05; pH of satd aq soln 9.8. One gram dissolves in 120 ml water, 60 ml water at 80°, 2 ml alcohol, 1.2 ml hot alcohol, 13 ml benzene, 18 ml ether, 0.5 ml chloroform; freely sol in amyl alcohol, methanol, dil acids. Almost insol in petr ether or in soln of alkali hydroxides.

Acetate, $C_{20}H_{23}NO_5$. Dihydrate, crystals; acetic acid odor. Sol in water, alc. Loses acetic acid on keeping, then becomes incompletely sol in water. *Keep tightly closed.*

Hydrobromide, $C_{18}H_{21}NO_3$·HBr. Dihydrate, crystals. Anhydr, mp 190-192° [α]$_D^{25}$ −96.6°. One gram dissolves in 60 ml water, 110 ml alcohol. pH about 5.

Hydrochloride, $C_{18}H_{21}NO_3$·HCl. Dihydrate, small needles, mp ~280° with some decompn. [α]$_D^{25}$ −108°. One gram dissolves in 20 ml water, 1 ml boiling water, 180 ml alcohol. pH about 5. LD_{50} s.c. in mice: 300 mg/kg (Eddy, Sumwalt).

Salicylate, $C_{25}H_{25}NO_6$, white, crystalline powder. Slightly sol in water; freely sol in alcohol or ether.

Caution: May be habit forming. This is a controlled substance (opiate) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1995).

THERAP CAT: Analgesic (narcotic); antitussive.

THERAP CAT (VET): Analgesic (narcotic); antitussive.

2526. Codeine Methyl Bromide. Eucodin. $C_{19}H_{24}BrNO_3$; mol wt 394.31. C 57.88%, H 6.13%, Br 20.26%, N 3.55%, O 12.17%. $C_{19}H_{21}NO_3$·CH_3Br.

Crystals, mp ~260°. Sol in 2-3 parts water, in hot methanol, sparingly in alc. Insol in chloroform, ether.

Caution: May be habit forming. This is a controlled substance (opium derivative) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1, 1308.11 (1995).

THERAP CAT: Analgesic (narcotic); antitussive.

2527. Codeine *N*-Oxide. Genocodeine; genkodein; Codeigene. $C_{18}H_{21}NO_4$; mol wt 315.37. C 68.55%, H 6.71%, N 4.44%, O 20.29%. Prepn from codeine and 30% hydrogen peroxide: Freund, Speyer, *Ber.* **43,** 3313 (1910); Kelentey *et al., Arzneimittel-Forsch.* **7,** 594 (1957).

Platelets from water, mp 231-232°.

Monohydrate, crystals from alc, mp 215°. [α]$_D^{18}$ −97.1° (c = 2.1 in water).

Hydrochloride monohydrate, $C_{18}H_{21}NO_4$·HCl·H_2O, crystals, loses crystal water at 110°, mp 219-220°. [α]$_D^{20}$ −105.8° (c = 2 in water). One gram dissolves in 9.5 ml water.

Note: This is a controlled substance (opium derivative) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.11 (1995).

THERAP CAT: Antitussive.

2528. Codeine Phosphate. Galcodine. $C_{18}H_{24}NO_7P$; mol wt 397.36. C 54.41%, H 6.09%, N 3.52%, O 28.18%, P 7.79%.

Sesquihydrate, very efflorescent, small crystals or cryst powder. One gram dissolves in 2.3 ml water, 0.5 ml water at 80°, 325 ml alcohol, 125 ml boiling alcohol, 4500 ml chloroform, 1875 ml ether. pH of a 2% aq soln: 4.6. *Keep well closed.*

Note: This is a controlled substance (opiate) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.12 (1995).

THERAP CAT: Analgesic (narcotic); antitussive.

THERAP CAT (VET): Analgesic (narcotic); antitussive.

2529. Codeine Sulfate. $C_{36}H_{42}N_2O_{10}S$; mol wt 696.82. C 62.05%, H 6.36%, N 4.02%, O 22.96%, S 4.60%.

Trihydrate, crystals or cryst powder. One gram dissolves in 30 ml water, 6.5 ml water at 80°, 1300 ml alc. Insol in chloroform or ether. pH: 5.0. Store in airtight containers; protect from light.

Note: This is a controlled substance (opiate) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.12 (1995).

THERAP CAT: Analgesic (narcotic); antitussive.

THERAP CAT (VET): Analgesic (narcotic); antitussive

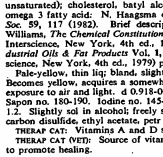
2530. Cod Liver Oil. Gadaol; Tunol. The partially destearinated fixed oil expressed from fresh livers of *Gadus morrhua* L., and other species of *Gadidae. Constit.* Most important are vitamins A and D, each gram containing at least 850 U.S.P. units vitamin A (255 μg) and at least 85 U.S.P. units vitamin D (2.125 μg); glycerides of palmitic, stearic, etc. acids (≤19% saturated fatty acids; remainder unsaturated); cholesterol; butyl alcohol esters. Source of omega 3 fatty acid: N. Haagsma *et al., J. Am. Oil Chem. Soc.* **59,** 117 (1982). Brief description: D. Hilditch, P. Williams, *The Chemical Constitution of Natural Fats* (Wiley-Interscience, New York, 4th ed., 1964) p 43; *Bailey's Industrial Oils & Fat Products* Vol. **1,** D. Swern (Wiley-Interscience, New York, 4th ed., 1979) pp 451-453.

Pale-yellow, thin liq; bland, slightly fishy taste and odor. Becomes yellow, acquires a somewhat disagreeable odor on exposure to air and light. d_{15}^{15} 0.918-0.927. n_D^{25} 1.4705-1.4745. Sapon no. 180-190. Iodine no. 145-180. Acid no. not over 1.2. Slightly sol in alcohol; freely sol in chloroform, ether, carbon disulfide, ethyl acetate, petr ether.

THERAP CAT: Vitamins A and D source.

THERAP CAT (VET): Source of vitamins A and D. Locally to promote healing.

2531. Coenzyme A. CoA. $C_{21}H_{36}N_7O_{16}P_3S$; mol wt 767.54. C 32.86%, H 4.73%, N 12.77%, O 33.35%, P 12.11%, S 4.18%. An essential cofactor in enzymatic acetyl transfer reactions. Synthesized in cells from pantothenate, ATP and cysteine. Found ubiquitously in mammalian cells. Isoln from animal sources: Lipmann *et al., J. Biol. Chem.* **167,** 869 (1947); **186,** 235 (1950). Many microorganisms contain large amounts of the coenzyme. Isoln from *Streptomyces fradiae:* Kaplan, Lipmann, *ibid.* **174,** 37 (1948). Purifications: De Vries *et al., J. Am. Chem. Soc.* **72,** 4838 (1950); Gregory *et al., ibid.* **74,** 854 (1952). Structure: Baddiley *et al., Nature* **171,** 76 (1953). Total synthesis: Moffatt, Khorana, *J. Am. Chem. Soc.* **81,** 1265 (1959); **83,** 663 (1961); Shimizu *et al., Chem. Pharm. Bull.* **13,** 1142 (1965). Reviews: Lipmann, *Bacteriol. Rev.* **17,** 1-16 (1953); Baddiley, *Advan. Enzymol.* **16,** 1 (1955); Jaenicke, Lynen in *The Enzymes* vol. **3,** P. D. Boyer *et al.,* Eds. (Academic Press, New York, 2nd ed., 1960) pp 3-103. Review of metabolism: J. D. Robishaw, J. R. Neely, *Am. J. Physiol.* **248,** E1-E9 (1985); of clinical evaluations in hyperlipoproteinemia: A.



APPENDIX C:
RELATED PROCEEDINGS

No related proceedings are pending.